

PROTEINS AND NUCLEIC ACIDS ENCODING SAME**RELATED APPLICATIONS**

This application claims priority from U.S.S.N. 60/253,834, filed November 29, 2000; U.S.S.N. 60/250,926, filed November 30, 2000; U.S.S.N. 60/264,180, filed January 25, 2001; 5 U.S.S.N. 60/274,194, filed March 8, 2001; U.S.S.N. 60/313,656, filed August 20, 2001; and U.S.S.N. 60/327,456, filed October 5, 2001 each of which is incorporated by reference in its entirety.

FIELD OF THE INVENTION

10 The invention generally relates to nucleic acids and polypeptides encoded thereby.

BACKGROUND OF THE INVENTION

The invention generally relates to nucleic acids and polypeptides encoded therefrom. More specifically, the invention relates to nucleic acids encoding cytoplasmic, nuclear, 15 membrane bound, and secreted polypeptides, as well as vectors, host cells, antibodies, and recombinant methods for producing these nucleic acids and polypeptides.

SUMMARY OF THE INVENTION

The invention is based in part upon the discovery of nucleic acid sequences encoding 20 novel polypeptides. The novel nucleic acids and polypeptides are referred to herein as NOVX, or NOV1, NOV2, NOV3, NOV4, NOV5, NOV6, NOV7, NOV8, NOV9, NOV10, NOV11, and NOV12 nucleic acids and polypeptides. These nucleic acids and polypeptides, as well as derivatives, homologs, analogs and fragments thereof, will hereinafter be collectively designated as "NOVX" nucleic acid or polypeptide sequences.

25 In one aspect, the invention provides an isolated NOVX nucleic acid molecule encoding a NOVX polypeptide that includes a nucleic acid sequence that has identity to the nucleic acids disclosed in SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, and 217. In some embodiments, the NOVX nucleic acid molecule will hybridize under stringent conditions to a nucleic acid sequence complementary to a nucleic acid molecule that 30 includes a protein-coding sequence of a NOVX nucleic acid sequence. The invention also

includes an isolated nucleic acid that encodes a NOVX polypeptide, or a fragment, homolog, analog or derivative thereof. For example, the nucleic acid can encode a polypeptide at least 80% identical to a polypeptide comprising the amino acid sequences of SEQ ID NOS:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, and 218. The nucleic acid can be, for example, a genomic DNA fragment or a cDNA molecule that includes the nucleic acid sequence of any of SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, and 217.

Also included in the invention is an oligonucleotide, *e.g.*, an oligonucleotide which includes at least 6 contiguous nucleotides of a NOVX nucleic acid (*e.g.*, SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, and 217) or a complement of said oligonucleotide.

Also included in the invention are substantially purified NOVX polypeptides (SEQ ID NOS:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, and 218). In certain embodiments, the NOVX polypeptides include an amino acid sequence that is substantially identical to the amino acid sequence of a human NOVX polypeptide.

The invention also features antibodies that immunoselectively bind to NOVX polypeptides, or fragments, homologs, analogs or derivatives thereof.

In another aspect, the invention includes pharmaceutical compositions that include therapeutically- or prophylactically-effective amounts of a therapeutic and a pharmaceutically-acceptable carrier. The therapeutic can be, *e.g.*, a NOVX nucleic acid, a NOVX polypeptide, or an antibody specific for a NOVX polypeptide. In a further aspect, the invention includes, in one or more containers, a therapeutically- or prophylactically-effective amount of this pharmaceutical composition.

In a further aspect, the invention includes a method of producing a polypeptide by culturing a cell that includes a NOVX nucleic acid, under conditions allowing for expression of the NOVX polypeptide encoded by the DNA. If desired, the NOVX polypeptide can then be recovered.

In another aspect, the invention includes a method of detecting the presence of a NOVX polypeptide in a sample. In the method, a sample is contacted with a compound that selectively binds to the polypeptide under conditions allowing for formation of a complex between the polypeptide and the compound. The complex is detected, if present, thereby identifying the NOVX polypeptide within the sample.

The invention also includes methods to identify specific cell or tissue types based on their expression of a NOVX.

Also included in the invention is a method of detecting the presence of a NOVX nucleic acid molecule in a sample by contacting the sample with a NOVX nucleic acid probe or primer, and detecting whether the nucleic acid probe or primer bound to a NOVX nucleic acid molecule in the sample.

5 In a further aspect, the invention provides a method for modulating the activity of a NOVX polypeptide by contacting a cell sample that includes the NOVX polypeptide with a compound that binds to the NOVX polypeptide in an amount sufficient to modulate the activity of said polypeptide. The compound can be, *e.g.*, a small molecule, such as a nucleic acid, peptide, polypeptide, peptidomimetic, carbohydrate, lipid or other organic (carbon
10 containing) or inorganic molecule, as further described herein.

Also within the scope of the invention is the use of a therapeutic in the manufacture of a medicament for treating or preventing disorders or syndromes including, *e.g.*, cardiomyopathy, atherosclerosis, hypertension, congenital heart defects, aortic stenosis, atrial
15 septal defect (ASD), atrioventricular (A-V) canal defect, ductus arteriosus, pulmonary stenosis, subaortic stenosis, ventricular septal defect (VSD), valve diseases, hypercoagulation, hemophilia, idiopathic thrombocytopenic purpura, heart failure, secondary pathologies caused by heart failure and hypertension, hypotension, angina pectoris, myocardial infarction, tuberosus sclerosis, scleroderma, transplantation, autoimmune disease, lupus erythematosus, viral/bacterial/parasitic infections, multiple sclerosis, autoimmune disease, allergies,
20 immunodeficiencies, graft versus host disease, asthma, emphysema, ARDS, inflammation and modulation of the immune response, viral pathogenesis, aging-related disorders, Th1 inflammatory diseases such as rheumatoid arthritis, multiple sclerosis, inflammatory bowel diseases, AIDS, wound repair, obesity, diabetes, endocrine disorders, anorexia, bulimia, renal artery stenosis, interstitial nephritis, glomerulonephritis, polycystic kidney disease, systemic,
25 renal tubular acidosis, IgA nephropathy, nephrological diseases, hypercalcaemia, Lesch-Nyhan syndrome, Von Hippel-Lindau (VHL) syndrome, trauma, regeneration (*in vitro* and *in vivo*), Hirschsprung's disease, Crohn's Disease, appendicitis, endometriosis, laryngitis, psoriasis, actinic keratosis, acne, hair growth/loss, alopecia, pigmentation disorders, myasthenia gravis, alpha-mannosidosis, beta-mannosidosis, other storage disorders,
30 peroxisomal disorders such as Zellweger syndrome, infantile Refsum disease, rhizomelic chondrodysplasia (chondrodysplasia punctata, rhizomelic), and hyperpipecolic acidemia, osteoporosis, muscle disorders, urinary retention, Albright Hereditary Osteodystrophy, ulcers, Alzheimer's disease, stroke, Parkinson's disease, Huntington's disease, cerebral palsy, epilepsy, Lesch-Nyhan syndrome, multiple sclerosis, ataxia-telangiectasia, behavioral

disorders, addiction, anxiety, pain, neuroprotection, Stroke, Aphakia, neurodegenerative disorders, neurologic disorders, developmental defects, conditions associated with the role of GRK2 in brain and in the regulation of chemokine receptors, encephalomyelitis, anxiety, schizophrenia, manic depression, delirium, dementia, severe mental retardation and
5 dyskinesias, Gilles de la Tourette syndrome, leukodystrophies, cancers, breast cancer, CNS cancer, colon cancer, gastric cancer, lung cancer, melanoma, ovarian cancer, pancreatic cancer, kidney cancer, colon cancer, prostate cancer, neuroblastoma, and cervical cancer, Neoplasm; adenocarcinoma, lymphoma; uterus cancer, benign prostatic hypertrophy, fertility, control of growth and development/differentiation related functions such as but not limited
10 maturation, lactation and puberty, reproductive malfunction, and/or other pathologies and disorders of the like.

The therapeutic can be, *e.g.*, a NOVX nucleic acid, a NOVX polypeptide, or a NOVX-specific antibody, or biologically-active derivatives or fragments thereof.

For example, the compositions of the present invention will have efficacy for treatment
15 of patients suffering from the diseases and disorders disclosed above and/or other pathologies and disorders of the like. The polypeptides can be used as immunogens to produce antibodies specific for the invention, and as vaccines. They can also be used to screen for potential agonist and antagonist compounds. For example, a cDNA encoding NOVX may be useful in gene therapy, and NOVX may be useful when administered to a subject in need thereof. By
20 way of non-limiting example, the compositions of the present invention will have efficacy for treatment of patients suffering from the diseases and disorders disclosed above and/or other pathologies and disorders of the like.

The invention further includes a method for screening for a modulator of disorders or syndromes including, *e.g.*, the diseases and disorders disclosed above and/or other pathologies
25 and disorders of the like. The method includes contacting a test compound with a NOVX polypeptide and determining if the test compound binds to said NOVX polypeptide. Binding of the test compound to the NOVX polypeptide indicates the test compound is a modulator of activity, or of latency or predisposition to the aforementioned disorders or syndromes.

Also within the scope of the invention is a method for screening for a modulator of
30 activity, or of latency or predisposition to disorders or syndromes including, *e.g.*, the diseases and disorders disclosed above and/or other pathologies and disorders of the like by administering a test compound to a test animal at increased risk for the aforementioned disorders or syndromes. The test animal expresses a recombinant polypeptide encoded by a NOVX nucleic acid. Expression or activity of NOVX polypeptide is then measured in the test

animal, as is expression or activity of the protein in a control animal which recombinantly-expresses NOVX polypeptide and is not at increased risk for the disorder or syndrome. Next, the expression of NOVX polypeptide in both the test animal and the control animal is compared. A change in the activity of NOVX polypeptide in the test animal relative to the control animal indicates the test compound is a modulator of latency of the disorder or syndrome.

In yet another aspect, the invention includes a method for determining the presence of or predisposition to a disease associated with altered levels of a NOVX polypeptide, a NOVX nucleic acid, or both, in a subject (*e.g.*, a human subject). The method includes measuring the amount of the NOVX polypeptide in a test sample from the subject and comparing the amount of the polypeptide in the test sample to the amount of the NOVX polypeptide present in a control sample. An alteration in the level of the NOVX polypeptide in the test sample as compared to the control sample indicates the presence of or predisposition to a disease in the subject. Preferably, the predisposition includes, *e.g.*, the diseases and disorders disclosed above and/or other pathologies and disorders of the like. Also, the expression levels of the new polypeptides of the invention can be used in a method to screen for various cancers as well as to determine the stage of cancers.

In a further aspect, the invention includes a method of treating or preventing a pathological condition associated with a disorder in a mammal by administering to the subject a NOVX polypeptide, a NOVX nucleic acid, or a NOVX-specific antibody to a subject (*e.g.*, a human subject), in an amount sufficient to alleviate or prevent the pathological condition. In preferred embodiments, the disorder, includes, *e.g.*, the diseases and disorders disclosed above and/or other pathologies and disorders of the like.

In yet another aspect, the invention can be used in a method to identify the cellular receptors and downstream effectors of the invention by any one of a number of techniques commonly employed in the art. These include but are not limited to the two-hybrid system, affinity purification, co-precipitation with antibodies or other specific-interacting molecules.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, suitable methods and materials are described below. All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety. In the case of conflict, the

NOVX nucleic acids and their encoded polypeptides are useful in a variety of applications and contexts. The various NOVX nucleic acids and polypeptides according to the invention are useful as novel members of the protein families according to the presence of domains and sequence relatedness to previously described proteins. Additionally, NOVX
5 nucleic acids and polypeptides can also be used to identify proteins that are members of the family to which the NOVX polypeptides belong.

NOV1 is homologous to the transmembrane receptor UNC5H2-like family of proteins. Thus, NOV1 nucleic acids and polypeptides, antibodies and related compounds according to the invention will be useful in therapeutic and diagnostic applications implicated in, for
10 example; cardiomyopathy, atherosclerosis, hypertension, congenital heart defects, aortic stenosis, atrial septal defect (ASD), atrioventricular (A-V) canal defect, ductus arteriosus, pulmonary stenosis, subaortic stenosis, ventricular septal defect (VSD), valve diseases, tuberous sclerosis, scleroderma, obesity, transplantation, diabetes, autoimmune disease, renal artery stenosis, interstitial nephritis, glomerulonephritis, polycystic kidney disease, systemic
15 lupus erythematosus, renal tubular acidosis, IgA nephropathy, hypercalcaemia, Lesch-Nyhan syndrome, Von Hippel-Lindau (VHL) syndrome, Alzheimer's disease, stroke, tuberous sclerosis, Parkinson's disease, Huntington's disease, cerebral palsy, epilepsy, Lesch-Nyhan syndrome, multiple sclerosis, ataxia-telangiectasia, leukodystrophies, behavioral disorders, addiction, anxiety, pain, neuroprotection, cancers, and/or other pathologies and disorders. Also
20 since this gene is expressed at a measurably higher level in several cancer cell lines (including breast cancer, CNS cancer, colon cancer, gastric cancer, lung cancer, melanoma, ovarian cancer and pancreatic cancer), it may be useful in diagnosis and treatment of these cancers.

NOV2 is homologous to the protein tyrosine phosphatase precursor-like family of proteins. Thus NOV2 nucleic acids, polypeptides, antibodies and related compounds
25 according to the invention will be useful in therapeutic and diagnostic applications implicated in, for example; cancer, kidney cancer, trauma, regeneration (in vitro and in vivo), viral/bacterial/parasitic infections, nephrological diseases including diabetes, autoimmune disease, renal artery stenosis, interstitial nephritis, glomerulonephritis, polycystic kidney disease, systemic lupus erythematosus, renal tubular acidosis, IgA nephropathy,
30 hypercalcaemia, Lesch-Nyhan syndrome, Hirschsprung's disease, Crohn's Disease, appendicitis, and/or other pathologies and disorders.

NOV3 is homologous to the Human homolog of the Drosophila pecanex family of proteins. Thus NOV3 nucleic acids, polypeptides, antibodies and related compounds according to the invention will be useful in therapeutic and diagnostic applications implicated

in, for example; cancer, trauma, regeneration (in vitro and in vivo), viral/bacterial/parasitic infections, cardiomyopathy, atherosclerosis, hypertension, congenital heart defects, aortic stenosis, atrial septal defect (ASD), atrioventricular (A-V) canal defect, ductus arteriosus, pulmonary stenosis, subaortic stenosis, ventricular septal defect (VSD), valve diseases, 5 tuberosus sclerosis, multiple sclerosis, scleroderma, obesity, endometriosis, fertility, hypercoagulation, autoimmune disease, allergies, immunodeficiencies, transplantation, hemophilia, idiopathic thrombocytopenic purpura, graft versus host disease, Von Hippel-Lindau (VHL) syndrome, Alzheimer's disease, stroke, hypercalcaemia, Parkinson's disease, Huntington's disease, cerebral palsy, epilepsy, ataxia-telangiectasia, leukodystrophies, 10 behavioral disorders, addiction, anxiety, pain, neuroprotection, systemic lupus erythematosus, asthma, emphysema, ARDS, laryngitis, psoriasis, actinic keratosis, acne, hair growth/loss, alopecia, pigmentation disorders, endocrine disorders, diabetes, renal artery stenosis, interstitial nephritis, glomerulonephritis, polycystic kidney disease, systemic lupus erythematosus, renal tubular acidosis, IgA nephropathy, Lesch-Nyhan syndrome, and a variety 15 of kidney diseases and/or other pathologies and disorders.

NOV4 is homologous to a family of Aurora-related kinase 1-like proteins. Thus, the NOV4 nucleic acids and polypeptides, antibodies and related compounds according to the invention will be useful in therapeutic and diagnostic applications implicated in, for example: breast, ovarian, colon, prostate, neuroblastoma, and cervical cancer, Cardiomyopathy, 20 Atherosclerosis, Hypertension, Congenital heart defects, Aortic stenosis, Atrial septal defect (ASD), Atrioventricular (A-V) canal defect, Ductus arteriosus, Pulmonary stenosis, Subaortic stenosis, Ventricular septal defect (VSD), valve diseases, Tuberosus sclerosis, Scleroderma, Obesity, Transplantation, Diabetes, Von Hippel-Lindau (VHL) syndrome, Pancreatitis, Alzheimer's disease, Stroke, hypercalcaemia, Parkinson's disease, Huntington's disease, 25 Cerebral palsy, Epilepsy, Lesch-Nyhan syndrome, Multiple sclerosis, Ataxia-telangiectasia, Leukodystrophies, Behavioral disorders, Addiction, Anxiety, Pain, and Neuroprotection, and/or other pathologies.

NOV5 is homologous to the 26S protease regulatory subunit 4-like family of proteins. Thus, NOV5 nucleic acids, polypeptides, antibodies and related compounds according to the invention will be useful in therapeutic and diagnostic applications implicated in, for example: 30 cataract and Aphakia, Alzheimer's disease, neurodegenerative disorders, inflammation and modulation of the immune response, viral pathogenesis, aging-related disorders, neurologic disorders, cancer, and/or other pathologies.

NOV6 is homologous to the MITSUGUMIN29-like family of proteins. Thus, NOV6 nucleic acids, polypeptides, antibodies and related compounds according to the invention will be useful in therapeutic and diagnostic applications implicated in, for example: muscular dystrophy, Lesch-Nyhan syndrome, myasthenia gravis, diabetes, autoimmune disease, renal artery stenosis, interstitial nephritis, glomerulonephritis, polycystic kidney disease, systemic lupus erythematosus, renal tubular acidosis, IgA nephropathy, hypercalcaemia, cardiomyopathy, atherosclerosis, hypertension, congenital heart defects, aortic stenosis, atrial septal defect (ASD), atrioventricular (A-V) canal defect, ductus arteriosus, pulmonary stenosis, subaortic stenosis, ventricular septal defect (VSD), valve diseases, tuberous sclerosis, scleroderma, obesity, transplantation, adrenoleukodystrophy, congenital adrenal hyperplasia, and other diseases, disorders and conditions of the like. Also since the invention is highly expressed in one of the lung cancer cell lines (Lung cancer NCI-H522), it may be useful in diagnosis and treatment of this cancer.

NOV7 is homologous to the Wnt-15-like family of proteins. Thus NOV7 nucleic acids, polypeptides, antibodies and related compounds according to the invention will be useful in Von Hippel-Lindau (VHL) syndrome, Alzheimer's disease, stroke, tuberous sclerosis, hypercalcaemia, Parkinson's disease, Huntington's disease, cerebral palsy, epilepsy, Lesch-Nyhan syndrome, multiple sclerosis, ataxia-telangiectasia, leukodystrophies, behavioral disorders, addiction, anxiety, pain, neurodegeneration, cancer, developmental defects, and/or other pathologies/disorders.

NOV8 is homologous to members of the Wnt-14-like family of proteins. Thus, the NOV8 nucleic acids, polypeptides, antibodies and related compounds according to the invention will be useful in therapeutic and diagnostic applications implicated in, for example; Von Hippel-Lindau (VHL) syndrome, Alzheimer's disease, stroke, tuberous sclerosis, hypercalcaemia, Parkinson's disease, Huntington's disease, cerebral palsy, epilepsy, Lesch-Nyhan syndrome, multiple sclerosis, ataxia-telangiectasia, leukodystrophies, behavioral disorders, addiction, anxiety, pain, neurodegeneration, cancer, developmental defects, and/or other pathologies/disorders.

NOV9 is homologous to the beta adrenergic receptor kinase-like family of proteins. Thus, NOV9 nucleic acids and polypeptides, antibodies and related compounds according to the invention will be useful in therapeutic and diagnostic applications implicated in, for example: heart failure, hypertension, secondary pathologies caused by heart failure and hypertension, and other diseases, disorders and conditions of the like. Additionally, the compositions of the present invention may have efficacy for treatment of patients suffering

from conditions associated with the role of GRK2 in brain and in the regulation of chemokine receptors.

NOV10 is homologous to the alpha-mannosidase-like family of proteins. Thus, NOV10 nucleic acids and polypeptides, antibodies and related compounds according to the invention will be useful in therapeutic and diagnostic applications implicated in, for example: alpha-mannosidosis, beta-mannosidosis, other storage disorders, peroxisomal disorders such as zellweger syndrome, infantile refsum disease, rhizomelic chondrodysplasia (chondrodysplasia punctata, rhizomelic), and hyperpipecolic acidemia and other diseases, disorders and conditions of the like, and/or other pathologies/disorders.

NOV11 is homologous to the C1q-related factor-like family of proteins. Thus, NOV11 nucleic acids and polypeptides, antibodies and related compounds according to the invention will be useful in therapeutic and diagnostic applications implicated in, for example: Th1 inflammatory diseases such as rheumatoid arthritis, multiple sclerosis, inflammatory bowel diseases and psoriasis, lupus erythematosus and glomerulonephritis, control of growth and development/differentiation related functions such as but not limited maturation, lactation and puberty, osteoporosis, obesity, aging and reproductive malfunction and hence could be used in treatment and/or diagnosis of these disorders.

NOV12 is homologous to the Plexin-1 like family of proteins. Thus, NOV12 nucleic acids and polypeptides, antibodies, and related compounds according to the invention will be useful in therapeutic and diagnostic applications implicated in, for example: AIDS, cancer therapy, treatment of Neurologic diseases, Brain and/or autoimmune disorders like encephalomyelitis, neurodegenerative disorders, Alzheimer's Disease, Parkinson's Disorder, immune disorders, and hematopoietic disorders, endocrine diseases, muscle disorders, inflammation and wound repair, bacterial, fungal, protozoal and viral infections (particularly infections caused by HIV-1 or HIV-2), pain, cancer (including but not limited to Neoplasm; adenocarcinoma; lymphoma; prostate cancer; uterus cancer), anorexia, bulimia, asthma, Parkinson's disease, acute heart failure, hypotension, hypertension, urinary retention, osteoporosis, Crohn's disease; multiple sclerosis; and Treatment of Albright Hereditary Osteodystrophy, angina pectoris, myocardial infarction, ulcers, asthma, allergies, benign prostatic hypertrophy, and psychotic and neurological disorders, including anxiety, schizophrenia, manic depression, delirium, dementia, severe mental retardation and dyskinesias, such as Huntington's disease or Gilles de la Tourette syndrome, and/or other pathologies/disorders.

The NOVX nucleic acids and polypeptides can also be used to screen for molecules, which inhibit or enhance NOVX activity or function. Specifically, the nucleic acids and polypeptides according to the invention may be used as targets for the identification of small molecules that modulate or inhibit, *e.g.*, neurogenesis, cell differentiation, cell proliferation, hematopoiesis, wound healing and angiogenesis.

Additional utilities for the NOVX nucleic acids and polypeptides according to the invention are disclosed herein.

NOV1

NOV1 includes three novel transmembrane receptor UNC5H2-like proteins disclosed below. The disclosed sequences have been named NOV1a and NOV1b.

NOV1a

A disclosed NOV1a nucleic acid of 2860 nucleotides (also referred to as GMba58o1_A_da1) encoding a transmembrane receptor UNC5H2-like protein is shown in Table 1A. An open reading frame was identified beginning with an ATG initiation codon at nucleotides 59-61 and ending with a TGA codon at nucleotides 2858-2860. A putative untranslated region upstream from the initiation codon and downstream from the termination codon is underlined in Table 1A. The start and stop codons are in bold letters.

Table 1A. NOV1a nucleotide sequence (SEQ ID NO:1).

<p>AGACTGGGGCCAGGGAGACAGCCCTGGGGGAGAGGCGCCGAAACCAGGCCGCGGAGCATGGGGGCCCGGAG CGGAGCTCGGGGCGCGCTGCTGCTGGCACTGCTGCTGCTGCTGGGACCCGAGGCTGAGCCAAAGCAGGCACTGA TTCTGGCAGCGAGGTGCTCCCTGACTCCTTCCCGTCAGCGCCAGCAGAGCCGCTGCCCTACTTCCTGCAGGA GCCACAGGACGCCCTACATTGTGAAGAAACAAGCCTGTGGAGCTCCGCTGCCGCGCCTTCCCCGCCACACAGAT CTACTTCAAGTGCAACGCGCAGTGGGTGAGCCAGAACGACCAGTCAACAGGAAGGCCCTGGATGAGGCCAC CGGTCTGCGGGTGCGCGAGGTGCAGATCGAGGTGTCGCGGCAGCAGGTGGAGGAGCTCTTGGGCTGGAGGA TTACTGGTGCCAGTGGCTGGCCTGGAGCTCCGCGGGCACCACCAAGAGTCGCCGAGCCTACGTCCGCATCGC CTACCTGCGCAAGAACTTCGATCAGGAGCCTCTGGGCAAGGAGGTGCCCTGGACCATGAGGTTCTCCTGCA GTGCCGCCCGCGGAGGGGGTGCCTGTGGCCGAGGTGGAATGGCTCAAGAATGAGGATGTCATCGACCCAC CCAGGACACCAACTTCTGCTCACCATCGACCACAACCTCATCATCCGCCAGGCCCGCCTGTCGGACACTGC CAACTATACCTGCGTGGCCAAGAATCATCGTGGCCAAACGCCGAGCACCCTGCCACCGTCATCGTCTACGT GAATGGCGGGTGGTCCAGCTGGGCAGAGTGGTCAACCTGCTCAACCGCTGTGGCCGAGGCTGGCAGAAGCG CACCCGGACCTGCACCAACCCCGCTCCACTCAACGAGGGGCTTCTGCGAGGGCCAGGCATTCCAGAAGAC CGCCTGCACCAACCATCTGCCAGTCCGATGGGGCGTGGACGGAGTGGAGCAAGTGGTCAGCCTGCAGCACTGA GTGTGCCCACTGGCGTAGCCGCGAGTGCATGGCGCCCCACCCAGAACGAGGCCGTGACTGCAGCGGGAC GCTGCTCGACTCTAAGAACTGCACAGATGGGCTGTGCATGCAACTGGAGGCCCTCAGGGGATGCGGCGCTGTA TGCGGGGCTCGTGGTGGCCATCTTCGTGGTCTGGCAATCCTCATGGCGGTGGGGTGGTGGTACCGCCG CAACTGCCGTGACTTCGACACAGACATCACTGACTCATCTGCTGCCCTGACTGGTGGTTTCCACCCCGTCAA CTTTAAGACGGCAAGGCCAGTAAACCGCAGCTCCTACACCCCTCTGTGCCTCCTGACCTGACAGCCAGCGC CGGCATCTACCGCGGACCCGTGTATGCCCTGCAGGACTCCACCGACAAAATCCCCATGACCAACTCTCTCT GCTGGACCCCTTACCCAGCCTTAAGGTCAAGTCTACAGCTCCAGCACCACGGGCTCTGGGCCAGGCCTGGC AGATGGGGCTGACCTGCTGGGGTCTTGCCTGCTGGCAGATACCCCTAGCGATTTCGCCCGGGACACCCACTT CCTGCACCTGCGCAGCGCCAGCCTCGGTTCCAGCAGCTCTTGGGCTGCCCGGAGACCCAGGAGCAGCGT CAGCGGCACCTTTGGCTGCTGGGTGGGAGGCTCAGCATCCCGGCAAGGGGTCAGTGTGCTGGTCCCAA TGGAGCCATTCCCGAGGGCAAGTTCTACGAGATGTATCTACTCATCAACAAGGCAGAAAGTACCTGCCGCT TTCAGAAGGGACCCAGACAGTATTGAGCCCTCGGTGACCTGTGGACCCACAGGCCTCCTGCTGTGCCGCC</p>
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CGTCATCCTCACCATGCCCCACTGTGCCGAAGTCAGTGCCCGTGACTGGATCTTTCAGCTCAAGACCCAGGC
CCACCAGGGCCACTGGGAGGAGGTGGTGACCCCTGGATGAGGAGACCCTGAACACACCCTGCTACTGCCAGCT
GGAGCCAGGGCCTGTACATCCTGCTGGACCAGCTGGGCACCTACGTGTTACGCGGAGTCTATTCCCG
CTCAGCAGTCAAGCGGCTCCAGCTGGCCGCTCTCGCCCCCGCCCTCTGCACCTCCCTGGAGTACAGCCTCCG
GGTCTACTGCCTGGAGGACACGCCTGTAGCACTGAAGGAGGTGCTGGAGCTGGAGCGGACTCTGGCGGATA
CTTGGTGGAGGAGCCGAAACCGCTAATGTTCAAGGACAGTTACCACAACCTGCGCCTCTCCCTCCATGACCT
CCCCCATGCCATTGGAGGAGCAAGCTGCTGGCCAAATACCAGGAGATCCCTTCTATCACATTGGAGTGG
CAGCCAGAAGGCCCTCCACTGCACTTTCACCTGGAGAGGCACAGCTTGGCCTCCACAGAGCTCACCTGCAA
GATCTGCGTGGCGCAAGTGAAGGGGAGGGCCAGATATTCCAGCTGCATACCACTCTGGCAGAGACACCTGC
TGGCTCCCTGGACACTCTCTGCTCTGCCCCCTGGCAGCACTGTCAACCCAGCTGGGACCTTATGCCTTCAA
GATCCCACTGTCCATCCGCCAGAAGATATGCAACAGCCTAGATGCCCCCACTCACGGGGCAATGACTGGCG
GATGTTAGCACAGAAGCTCTCTATGGACCGGTACCTGAATTACTTTGCCACCAAAGCGAGCCCCACGGGTGT
GATCCTGGACCTCTGGGAAGCTCTGCGAGGAGCATGGGGACCTCAACAGCCTGGCGAGTGCCTTGGAGGA
GATGGGCAAGAGTGAGATGCTGGTGGCTGTGGCCACCGACGGGGACTGCTGA
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In a search of public sequence databases, the NOV1a nucleic acid sequence, located on chromosome 10 has 1604 of 1895 bases (84%) identical to a transmembrane receptor UNC5H2 mRNA from *Rattus Norvegicus*, (GENBANK-ID: RNU87306). Public nucleotide databases include all GenBank databases and the GeneSeq patent database.

In all BLAST alignments herein, the "E-value" or "Expect" value is a numeric indication of the probability that the aligned sequences could have achieved their similarity to the BLAST query sequence by chance alone, within the database that was searched. For example, the probability that the subject ("Sbjct") retrieved from the NOV1a BLAST analysis, e.g., transmembrane receptor UNC5H2 mRNA from *Rattus Norvegicus*, matched the Query NOV1a sequence purely by chance is 0.0. The Expect value (E) is a parameter that describes the number of hits one can "expect" to see just by chance when searching a database of a particular size. It decreases exponentially with the Score (S) that is assigned to a match between two sequences. Essentially, the E value describes the random background noise that exists for matches between sequences.

The Expect value is used as a convenient way to create a significance threshold for reporting results. The default value used for blasting is typically set to 0.0001. In BLAST 2.0, the Expect value is also used instead of the P value (probability) to report the significance of matches. For example, an E value of one assigned to a hit can be interpreted as meaning that in a database of the current size one might expect to see one match with a similar score simply by chance. An E value of zero means that one would not expect to see any matches with a similar score simply by chance. See, e.g., <http://www.ncbi.nlm.nih.gov/Education/BLASTinfo/>. Occasionally, a string of X's or N's will result from a BLAST search. This is a result of automatic filtering of the query for low-complexity sequence that is performed to prevent artifactual hits. The filter substitutes any low-complexity sequence that it finds with the letter "N" in nucleotide sequence (e.g., "NNNNNNNNNNNNNN") or the letter "X" in protein sequences (e.g., "XXXXXXXXXX").

Low-complexity regions can result in high scores that reflect compositional bias rather than significant position-by-position alignment. (Wootton and Federhen, *Methods Enzymol* 266:554-571, 1996).

The disclosed NOV1a polypeptide (SEQ ID NO:2) encoded by SEQ ID NO:1 has 933 amino acid residues and is presented in Table 1B using the one-letter amino acid code. Signal P, Psort and/or Hydropathy results predict that NOV1a has a signal peptide at the first 26 amino acids and is likely to be localized at the plasma membrane with a certainty of 0.5140. In other embodiments, NOV1a is likely to be localized to the microbody (peroxisome) with a certainty of 0.1064, to the endoplasmic reticulum (membrane) with a certainty of 0.1000, or to the endoplasmic reticulum (lumen) with a certainty of 0.1000. The most likely cleavage site for NOV1a is between positions 26 and 27: SQA-GT

Table 1B. Encoded NOV1a protein sequence (SEQ ID NO:2).

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MGARSGARGALLLALLCWDPRLSQAGTDSGSEVLDPDSFSPAPAEPLPYFLQEPQDAYIVKNKPVELRCRAF
PATQIYFKCNGEWSQNDHVTQEGLEATGLRVREVQIEVSRQQVEELFGLLEDYWCQCVAWSSAGTTKSRRA
YVRIAYLRKNFDQEPLGKEVPLDHEVLLQCRPPEGVPVAEVEWLKNEVDIDPTQDTNFLTIDHNLIIIRQAR
LSDTANYTCVAKNIVAKRRSTTATVIVVYVNGGWSSWAESWPCSNRCGRGWQKRTRTCTNPAPLNGGAFCEGQ
AFQKTACTTICPVDGAWTEWSKWSACSTECAHWRSRECMAPPQNGGRDCSGTLLDSKNCTDGLCMQLEASG
DAALYAGLVVAIFVVVAIILMAVGVVVYRRNCRDFDITDSSAALTGGFHPVNFKTARPSNFPQLLHPSVPPD
LTASAGIYRGPVYALQDSTDKIPMTNSPLLDPLPSLVKVYSSSTTGSGPGLADGADLLGLVPPGTYPSPDFA
RDTHFLHLRSASLGSQQLLGLPRDPGSSVSGTFGCLGGRLSIPGTGVSLLVPNGAIPQGFYEMYLLINKAE
STLPLSEGTQTVLSPSVTCGPTGLLLCRPVILTMPHCAEVSARDWIFQLKTQAHQGHWEVVTLDEETLNTP
CYCQLEPRACHILLDQLGTYVFTGESYSRSVAVKRLQLAVFAPALCTSLEYSRLVYCLEDTPVALKEVLELER
TLGGYLVEEPKPLMFKDSYHNLRLSLHDLPHAHWSKLLAKYQEIPFYHIWSGSQKALHCTFTLERHSLAST
ELTCKICVRQVEGEGQIFQLHTTLAETPAGSLDTLCSAPGSTVTTQLGPYAFKIPLSIRQKICNSLDAPNSR
GNDWRMLAQKLSMDRYLNYFATKASPTGVILDLWEALQDDGDLNSLASALEEMGKSEMLVAVATDGDC
```

A search of sequence databases reveals that the NOV1a amino acid sequence has 862 of 945 amino acid residues (91%) identical to, and 897 of 945 amino acid residues (94%) similar to, the 945 amino acid residue 6330415E02RIK protein from *Mus musculus* (Q9D398) (E = 0.0). Public amino acid databases include the GenBank databases, SwissProt, PDB and PIR.

NOV1a is at least expressed in endothelial cells, heart, kidney, adipose, brain (hippocampus), brain (thalamus), cerebral cortex, and the following cancer cell lines: breast cancer, CNS cancer, colon cancer, gastric cancer, lung cancer, melanoma, ovarian cancer and pancreatic cancer at a measurably higher level than the following tissues: adrenal gland, bladder, bone marrow, brain (amygdala), brain (cerebellum), brain (whole), breast, colorectal, liver, lung, lymph node, mammary gland, ovary, pancreas, pituitary gland, placenta, prostate, salivary gland, skeletal muscle, small intestine, spinal cord, spleen, stomach, testis, thymus, thyroid gland, trachea, and uterus.

NOV1b

A disclosed NOV1b nucleic acid of 2860 nucleotides (also referred to as CG50126-02) encoding a novel beta-adrenergic receptor kinase-like protein is shown in Table 1C. An open reading frame was identified beginning with an ATG codon at nucleotides 59-61, and ending with a TGA codon at nucleotides 2858-2860. Putative untranslated regions, if any, are located upstream from the initiation codon and downstream from the termination codon.

Table 1C. NOV1b nucleotide sequence (SEQ ID NO:3).

AGACTGGGGCCAGGGAGACAGCCCTGGGGGAGAGGCGCCCGAACCAGGCCGCGGAACATGGGGGCCGAGCGGAGCTC
GGGGCGCGCTGCTGCTGGCACTGCTGCTCTGCTGGGACCCGAGGCTGAGCCAAGCAGGCACTGATTCCTGGCAGCGAGGTG
CTCCCTGACTCCTTCCCGTCAGCGCCAGCAGAGCGCTGCCTACTTCCTGCAGGAGCCACAGGACGCCTACATTGTGAA
GAACAAGCCTGTGGAGCTTCGCTGCCGCGCCTTCCCGCCACACAGATCTACTCAAGTGCAACGCGAGTGGGTACGCC
AGAACGACCACGTACACAGGAAGCCCTGGATGAGGCCACCGGCCCTGCGGGTGCGCGAGGTGCAGATCGAGGTGTCGCGG
CAGCAGGTGGAGGAGCTCTTTGGGCTGGAGGATTACTGGTGCCAGTGCGTGGCTGGAGCTCCGCGAGGCACCACCAAGAG
TCGCGGAGCCTACGTCCGCTACCTGCGCAAGAACTTCGATCAGGAGCCTCTGGGCAAGGAGGTGCCCTTGGACC
ATGAGGTTCTCTGCACTGCCGCCCGCGGAGGGGTGCTGTGGCCGAGGTGGAATGGCTCAAGAATGAGGATGTCAATC
GACCCACCCAGGACACCAACTTCCTGCTCACCATCGACCAACCTCATCATCCGCCAGGCCCGCTGTCCGCACTGC
CAACTATACCTGCGTGGCCAAAGAACATCGTGGCCAAACGCGGAGCACCACTGCCACCGTCATCGTCTACGTGAATGGCG
GCTGGTCCAGCTGGGCAGAGTGGTCACTGCTCCAAACCGCTGTGGCCGAGGTGGCAGAAGCGCACCCGGACCTGCACC
AACCCGCTCCTCACTCAACGAGGGGCTTCTGCGAGGGGCCAGGCATTCCAGAAGACCGCTGCACCACCTATCTGCCAGT
CGATGGGGCGTGGACGAGTGGAGCAAGTGGTCAAGCTGCACTGAGTGTGCCACTGGCGTAGCCGCGAGTGGTGG
CGCCCCACCCAGAACCGGAGGCGGTGACTGCAGCGGACGCTGCTCGACTCTAAGAACTGCACAGATGGGCTGTGCATG
CAACTGGAGGCTCAGGGGATGCGGCGCTGTATGCGGGCTCGTGGTGGCCATCTTCGTGGTCTGTGGCAATCCTCATGGC
GGTGGGGGTGGTGGTGTACCGCCGCAACTGCCGTGACTTCGACACAGACATCACTGACTCATCTGCTGCCCTGACTGGTG
GTTTCCACCCCGTCACTTTAAGACGGCAAGGCCAGTAACCCGAGCTCCTACACCCCTCTGTGCTCCTGACCTGACA
GCCAGCGCCGCGATCTACCGCGGACCCGCTGTATGCCCTGCAGGACTCCACCGACAAAATCCCATGACCAACTCTCCTCT
GCTGGACCCCTTACCCAGCCTTAAGGTCAAGGTCTACAGCTCCAGCACCAAGGCTCTGGGCCAGGCCTGGCAGATGGGG
CTGACCTGCTGGGGTCTTGGCCGCTGGCACATACCTAGCGATTTGCGCCGGGACACCCACTTCTGCACTGCGCAGC
GCCAGCCTCGGTTCCAGCAGCTCTTGGGCTGCCCCGAGACCCAGGAGCAGCGTCAGCGGCACCTTTGGGTGCTGGG
TGGGAGGCTCAGCATCCCCGGCAAGGGGTGAGTGTGGTGGCCAAATGGAGCCATTCCCAGGGCAAGTTCTACGAGA
TGTATCTACTCATCAACAAGGCAGAAAGTACCCTGCCGCTTTCAGAAAGGACCCAGACAGTATTAGCCCCCTCGGTGACC
TGTGGACCCACAGGCCCTCTGCTGTGCCGCCCGCTCATCTCACCATGCCCACTGTGCCGAAGTCAGTGCCCGTGAATG
GATCTTTCAGCTCAAGACCCAGGCCACCGGGCCACTGGGAGGAGGTGGTGACCTGGATGAGGAGACCCCTGAACACAC
CCTGCTACTGCGAGCTGGAGCCCAGGGCCTGTACATCCTGCTGGACAGCTGGGCACCTACGTGTTACGCGGCGAGTCC
TATTCGCGCTCAGCAGTCAAGCGCTCCAGCTGGCCGCTCTTGGCCCCGCGCTCTGCACCTCCCTGGAGTACAGCCTCCG
GGTCTACTGCCTGGAGGACACGCTGTAGCACTGAAGGAGGTGCTGGAGCTGGAGCGGACTCTGGGCGGATACTTGGTGG
AGGAGCGGAAACCGCTAATGTTCAAGGACAGTTACCAACACTGCGGCTCTCCCTCCATGACCTCCCCATGCCATTGG
AGGAGCAAGCTGCTGGCCAAATACCAGGAGATCCCCTTCTATCATTGGAGTGGCAGCCAGAAGGCCCTCCACTGCAC
TTTACCCCTGGAGAGGCACAGCTTGGCCTCCACAGAGCTCACTGCAAGATCTGCGTGGGCAAGTGAAGGGGAGGGCC
AGATATTCCAGCTGCATACCACTCTGGCAGAGACACCTGCTGGCTCCCTGGACACTCTCTGCTCTGCCCTGGCAGCACT
GTCAACACCCAGCTGGGACCTTATGCCTTCAAGATCCCACTGTCCATCCGCCAGAAGATATGCAACAGCCTAGATGCCCC
CAACTCAGGGGCAATGACTGGCGGATGTTAGCACAGAAGCTCTATGGACCGGTACCTGAATTACTTTGCCACCAAG
CGAGCCCCACGGGTGTGATCTGGACCTCTGGGAAGCTCTGCAGCAGGACGATGGGGACCTCAACAGCCTGGCGAGTGCC
TTGGAGGAGATGGGCAAGAGTGAGATGCTGGTGGCTGTGGCCACCGACGGGACTGCTGA

In a search of public sequence databases, the NOV1b nucleic acid sequence, located on chromosome 10 has 1604 of 1895 bases (84%) identical to a gb:GENBANK-ID:RNU87306|acc:U87306.1 mRNA from *Rattus norvegicus* (*Rattus norvegicus* transmembrane receptor Unc5H2 mRNA, complete cds). (E = 0.0) Public nucleotide databases include all GenBank databases and the GeneSeq patent database.

The disclosed NOV1b polypeptide (SEQ ID NO:4) encoded by SEQ ID NO:3 has 933 amino acid residues and is presented in Table 1D using the one-letter amino acid code. Signal P, Psort and/or Hydropathy results predict that NOV1b has a signal peptide at the first 26 amino acids and is likely to be localized at the plasma membrane with a certainty of 0.5140. In other embodiments, NOV1b is likely to be localized to the microbody (peroxisome) with a certainty of 0.1064, to the endoplasmic reticulum (membrane) with a certainty of 0.1000, or to the endoplasmic reticulum (lumen) with a certainty of 0.1000. The most likely cleavage site for NOV1b is between positions 26 and 27: SQA-GT

A search of sequence databases reveals that the NOV1b amino acid sequence has 862 of 945 amino acid residues (91%) identical to, and 893 of 945 amino acid residues (94%) similar to, the 945 amino acid residue ptnr:SPTREMBL-ACC:O08722 protein from *Rattus norvegicus* (Rat) (Transmembrane Receptor UNC5H2) (E = 0.0). Public amino acid databases include the GenBank databases, SwissProt, PDB and PIR.

NOV1b is expressed in at least adrenal gland, bone marrow, brain - amygdala, brain - cerebellum, brain - hippocampus, brain - substantia nigra, brain - thalamus, brain -whole, fetal brain, fetal kidney, fetal liver, fetal lung, heart, kidney, lymphoma - Raji, mammary gland, pancreas, pituitary gland, placenta, prostate, salivary gland, skeletal muscle, small intestine, spinal cord, spleen, stomach, testis, thyroid, trachea, uterus. This information was derived by determining the tissue sources of the sequences that were included in the invention including but not limited to SeqCalling sources, Public EST sources, and/or RACE sources.

The disclosed NOV1a polypeptide has homology to the amino acid sequences shown in the BLASTP data listed in Table 1E.

Table 1E. BLAST results for NOV1a

Gene Index/ Identifier	Protein/ Organism	Length (aa)	Identity (%)	Positives (%)	Expect
ptnr:SPTREMBL- ACC:Q9D398	6330415E02RIK PROTEIN - Mus musculus (Mouse)	945	862/945 (91%)	897/945 (94%)	0.0
ptnr:SPTREMBL- ACC:O08722	TRANSMEMBRANE RECEPTOR UNC5H2	945	862/945 (91%)	893/945 (94%)	0.0
ptnr:SPTREMBL- ACC:O08747	UNC-5 HOMOLOG (C. ELEGANS)	931	610/929 (65%)	723/929 (77%)	0.0
ptnr:SPTREMBL- ACC:O95185	TRANSMEMBRANE RECEPTOR UNC5C - Homo sapiens	931	598/929 (64%)	718/929 (77%)	0.0

The homology between these and other sequences is shown graphically in the ClustalW analysis shown in Table 1F. In the ClustalW alignment of the NOV1 proteins, as well as all other ClustalW analyses herein, the black outlined amino acid residues indicate regions of conserved sequence (*i.e.*, regions that may be required to preserve structural or functional properties), whereas non-highlighted amino acid residues are less conserved and can potentially be altered to a much broader extent without altering protein structure or function.

Table 1F. ClustalW Analysis of NOV1

1)	NOV1a (SEQ ID NO:2)
2)	NOV1b (SEQ ID NO:4)
3)	ptnr: 6330415E02RIK PROTEIN - Mus musculus (Mouse) (SEQ ID NO:33)
4)	ptnr: TRANSMEMBRANE RECEPTOR UNC5H2 (SEQ ID NO:34)
5)	ptnr: UNC-5 HOMOLOG (C. ELEGANS) (SEQ ID NO:35)
6)	ptnr: TRANSMEMBRANE RECEPTOR UNC5C - Homo sapiens (SEQ ID NO:36)

NOV1a	-----MCARSGA- RGALLLALLLCWDPRLSQAGTDSQSE -----VLPDSFSPSAPAEPLPYFLQEPDAYIVNKKPVE	66
NOV1b	-----MCARSGA- RGALLLALLLCWDPRLSQAGTDSQSE -----VLPDSFSPSAPAEPLPYFLQEPDAYIVNKKPVE	66
Q9D398	-----MCARSGV- RSALLLALLLCWDPTFSLAGVDSAGQ -----VLPDSFSPSAPAEOLPYFLQEPDAYIVNKKPVE	66
O08722	-----MCARSGA- RGALLLALLLCWDPTFSLAGTDSQSE -----ALPDSFSPSAPAEOLPHFLIPEPDAYIVNKKPVE	66
O08747	MRKGLRATAAR CG LGIGYLLQMLPLPALALLSAGTGSAAQDDFFHELPE TFPSQPEPLPHFLI EPEDAYIVNKKPVN	80
O95185	MRKGLRATAAR CG LGIGYLLQMLPLPALALLSAGTGSAAQDDFFHELPE TFPSQPEPLPHFLI EPEDAYIVNKKPVN	80
NOV1a	LRCRAFPATQIYFKNGE WVSNQDHVTQ ESLDEATGLRVRE VOIEVSRQQVEELFGLEDYWCQCVAWSSAGTTKSRRAYV	146
NOV1b	LRCRAFPATQIYFKNGE WVSNQDHVTQ ESLDEATGLRVRE VOIEVSRQQVEELFGLEDYWCQCVAWSSAGTTKSRRAYV	146
Q9D398	LRCRAFPATQIYFKNGE WVSNQDHVTQ ESLDEATGLRVRE VOIEVSRQQVEELFGLEDYWCQCVAWSSAGTTKSRRAYV	146
O08722	LRCRAFPATQIYFKNGE WVSNQDHVTQ ESLDEATGLRVRE VOIEVSRQQVEELFGLEDYWCQCVAWSSAGTTKSRRAYV	146
O08747	LYCKASPATQIYFKNGE WVSNQDHVTQ ESLDEATGLRVRE VOIEVSRQQVEELFGLEDYWCQCVAWSSAGTTKSRRAYV	160
O95185	LYCKASPATQIYFKNGE WVSNQDHVTQ ESLDEATGLRVRE VOIEVSRQQVEELFGLEDYWCQCVAWSSAGTTKSRRAYV	160
NOV1a	RIAYLRKNFDQ EPLGKEVPLDHEVLLQCRPPEGVPVAEVEWLK NEDVIDPTQDTN FLLTIDHNLIIRQARLSDTANYTCV	226
NOV1b	RIAYLRKNFDQ EPLGKEVPLDHEVLLQCRPPEGVPVAEVEWLK NEDVIDPTQDTN FLLTIDHNLIIRQARLSDTANYTCV	226
Q9D398	RIAYLRKNFDQ EPLGKEVPLDHEVLLQCRPPEGVPVAEVEWLK NEDVIDPTQDTN FLLTIDHNLIIRQARLSDTANYTCV	226
O08722	RIAYLRKNFDQ EPLGKEVPLDHEVLLQCRPPEGVPVAEVEWLK NEDVIDPTQDTN FLLTIDHNLIIRQARLSDTANYTCV	226
O08747	RIAYLRKTFDQ EPLGKEVPLDHEVLLQCRPPEGVPVAEVEWLK NEDVIDPTQDTN FLLTIDHNLIIRQARLSDTANYTCV	240
O95185	RIAYLRKTFDQ EPLGKEVPLDHEVLLQCRPPEGVPVAEVEWLK NEDVIDPTQDTN FLLTIDHNLIIRQARLSDTANYTCV	240
NOV1a	AKNIVAKRRSTTAT VIYVYNGGWSWA EWSPCSNRC GRGWQK TRTCTNPAP LN GGAFCEGQAFQKTACTT ICPVDGAWT	306
NOV1b	AKNIVAKRRSTTAT VIYVYNGGWSWA EWSPCSNRC GRGWQK TRTCTNPAP LN GGAFCEGQAFQKTACTT ICPVDGAWT	306
Q9D398	AKNIVAKRRSTTAT VIYVYNGGWSWA EWSPCSNRC GRGWQK TRTCTNPAP LN GGAFCEGQAFQKTACTT ICPVDGAWT	306
O08722	AKNIVAKRRSTTAT VIYVYNGGWSWA EWSPCSNRC GRGWQK TRTCTNPAP LN GGAFCEGQAFQKTACTT ICPVDGAWT	306
O08747	AKNIVAKRRSTTAT VIYVYNGGWSWA EWSPCSNRC GRGWQK TRTCTNPAP LN GGAFCEGQAFQKTACTT ICPVDGAWT	320
O95185	AKNIVAKRRSTTAT VIYVYNGGWSWA EWSPCSNRC GRGWQK TRTCTNPAP LN GGAFCEGQAFQKTACTT ICPVDGAWT	320
NOV1a	BWSKWSACST EC AHWSRECMAPP PC NGGRDCSGTLLDSN CTDGLCMC-----LEASGDAALYAGLVVA HFV	374

5	NOV1b	EWSKWSACSTECAHWSRECMAPPONGGRDCSGTLLDSKNC	-----LEASGEALYAGLVVAIFV	374
	Q9D398	EWSKWSACSTECAHWSRECMAPPONGGRDCSGTLLDSKNC	-----LEASGEALYAGLVVAIFV	386
	008722	EWSKWSACSTECAHWSRECMAPPONGGRDCSGTLLDSKNC	-----LEASGEALYAGLVVAIFV	386
	008747	EWSKWSACSTECAHWSRECMAPPONGGRDCSGTLLDSKNC	-----LEASGEALYAGLVVAIFV	389
	095185	EWSKWSACSTECAHWSRECMAPPONGGRDCSGTLLDSKNC	-----LEASGEALYAGLVVAIFV	389
10	NOV1a	VVAILMAVGCVVYRRNCRDFDITDSSAALTGGFHPVNFKTARPSN	POLLHPSVPPDLTASAGIYRGPVYALQDSADKI	454
	NOV1b	VVAILMAVGCVVYRRNCRDFDITDSSAALTGGFHPVNFKTARPSN	POLLHPSVPPDLTASAGIYRGPVYALQDSADKI	454
	Q9D398	VVAILMAVGCVVYRRNCRDFDITDSSAALTGGFHPVNFKTARPSN	POLLHPSVPPDLTASAGIYRGPVYALQDSADKI	466
	008722	VVAILMAVGCVVYRRNCRDFDITDSSAALTGGFHPVNFKTARPSN	POLLHPSVPPDLTASAGIYRGPVYALQDSADKI	466
	008747	VVAILMAVGCVVYRRNCRDFDITDSSAALTGGFHPVNFKTARPSN	POLLHPSVPPDLTASAGIYRGPVYALQDSADKI	463
	095185	VVAILMAVGCVVYRRNCRDFDITDSSAALTGGFHPVNFKTARPSN	POLLHPSVPPDLTASAGIYRGPVYALQDSADKI	463
15	NOV1a	PMTNSPLLDPLPSLKIKVYSSSTIGSGGLADGADLLGVLPPTGTYPSDFARDTHFLHRSASLGSC	OLLGLPRDPCSSVS	534
	NOV1b	PMTNSPLLDPLPSLKIKVYSSSTIGSGGLADGADLLGVLPPTGTYPSDFARDTHFLHRSASLGSC	OLLGLPRDPCSSVS	534
	Q9D398	PMTNSPLLDPLPSLKIKVYSSSTIGSGGLADGADLLGVLPPTGTYPSDFARDTHFLHRSASLGSC	OLLGLPRDPCSSVS	546
	008722	PMTNSPLLDPLPSLKIKVYSSSTIGSGGLADGADLLGVLPPTGTYPSDFARDTHFLHRSASLGSC	OLLGLPRDPCSSVS	546
	008747	PMTNSPLLDPLPSLKIKVYSSSTIGSGGLADGADLLGVLPPTGTYPSDFARDTHFLHRSASLGSC	OLLGLPRDPCSSVS	533
	095185	PMTNSPLLDPLPSLKIKVYSSSTIGSGGLADGADLLGVLPPTGTYPSDFARDTHFLHRSASLGSC	OLLGLPRDPCSSVS	533
20	NOV1a	GTFGCLGGRLLIPGTGVSLLVPAIGAIPOGKFYEMYLINNAESTLPLSEGTQTVLSPSVTCGPTGLLLCRPVILTMHPCA		614
	NOV1b	GTFGCLGGRLLIPGTGVSLLVPAIGAIPOGKFYEMYLINNAESTLPLSEGTQTVLSPSVTCGPTGLLLCRPVILTMHPCA		614
	Q9D398	GTFGCLGGRLLIPGTGVSLLVPAIGAIPOGKFYEMYLINNAESTLPLSEGTQTVLSPSVTCGPTGLLLCRPVILTMHPCA		626
	008722	GTFGCLGGRLLIPGTGVSLLVPAIGAIPOGKFYEMYLINNAESTLPLSEGTQTVLSPSVTCGPTGLLLCRPVILTMHPCA		626
	008747	GTFGCLGGRLLIPGTGVSLLVPAIGAIPOGKFYEMYLINNAESTLPLSEGTQTVLSPSVTCGPTGLLLCRPVILTMHPCA		613
	095185	GTFGCLGGRLLIPGTGVSLLVPAIGAIPOGKFYEMYLINNAESTLPLSEGTQTVLSPSVTCGPTGLLLCRPVILTMHPCA		613
30	NOV1a	EVSARDWIFOLKTOAHQGHWEVVTLDEETLNTPCYCOLBPRACHILLDQLGTYVFTGESYSRSYSAVKRLQLAFAPALCT		694
	NOV1b	EVSARDWIFOLKTOAHQGHWEVVTLDEETLNTPCYCOLBPRACHILLDQLGTYVFTGESYSRSYSAVKRLQLAFAPALCT		694
	Q9D398	EVSARDWIFOLKTOAHQGHWEVVTLDEETLNTPCYCOLBPRACHILLDQLGTYVFTGESYSRSYSAVKRLQLAFAPALCT		706
	008722	EVSARDWIFOLKTOAHQGHWEVVTLDEETLNTPCYCOLBPRACHILLDQLGTYVFTGESYSRSYSAVKRLQLAFAPALCT		706
	008747	EVSARDWIFOLKTOAHQGHWEVVTLDEETLNTPCYCOLBPRACHILLDQLGTYVFTGESYSRSYSAVKRLQLAFAPALCT		693
	095185	EVSARDWIFOLKTOAHQGHWEVVTLDEETLNTPCYCOLBPRACHILLDQLGTYVFTGESYSRSYSAVKRLQLAFAPALCT		693
35	NOV1a	SLEYSLRVYCLEDTFVALKEVLELERTLGGYLVVEEPKALFFKDSYHNRLSLHD	PHAHWSKLLAKYQEI PFYHWSGS	774
	NOV1b	SLEYSLRVYCLEDTFVALKEVLELERTLGGYLVVEEPKALFFKDSYHNRLSLHD	PHAHWSKLLAKYQEI PFYHWSGS	774
	Q9D398	SLEYSLRVYCLEDTFVALKEVLELERTLGGYLVVEEPKALFFKDSYHNRLSLHD	PHAHWSKLLAKYQEI PFYHWSGS	786
	008722	SLEYSLRVYCLEDTFVALKEVLELERTLGGYLVVEEPKALFFKDSYHNRLSLHD	PHAHWSKLLAKYQEI PFYHWSGS	786
	008747	SLEYSLRVYCLEDTFVALKEVLELERTLGGYLVVEEPKALFFKDSYHNRLSLHD	PHAHWSKLLAKYQEI PFYHWSGS	773
	095185	SLEYSLRVYCLEDTFVALKEVLELERTLGGYLVVEEPKALFFKDSYHNRLSLHD	PHAHWSKLLAKYQEI PFYHWSGS	773
40	NOV1a	QKALHCTFTLERHSLASTELTCNLCVROVEGEGQIFQLHTTLAGTPAGSL	LCAPGSTVITQLGPYAFKIPLSIROKI	854
	NOV1b	QKALHCTFTLERHSLASTELTCNLCVROVEGEGQIFQLHTTLAGTPAGSL	LCAPGSTVITQLGPYAFKIPLSIROKI	854
	Q9D398	QKALHCTFTLERHSLASTELTCNLCVROVEGEGQIFQLHTTLAGTPAGSL	LCAPGSTVITQLGPYAFKIPLSIROKI	866
	008722	QKALHCTFTLERHSLASTELTCNLCVROVEGEGQIFQLHTTLAGTPAGSL	LCAPGSTVITQLGPYAFKIPLSIROKI	866
	008747	QKALHCTFTLERHSLASTELTCNLCVROVEGEGQIFQLHTTLAGTPAGSL	LCAPGSTVITQLGPYAFKIPLSIROKI	852
	095185	QKALHCTFTLERHSLASTELTCNLCVROVEGEGQIFQLHTTLAGTPAGSL	LCAPGSTVITQLGPYAFKIPLSIROKI	852
50	NOV1a	CNSLDAPNSRGNDWRMLAQKLSMDRYLNYFATKASPTGVILDLWEALQDDGDLNS	SASALEEMGKSEMLVANATDGDG	933
	NOV1b	CNSLDAPNSRGNDWRMLAQKLSMDRYLNYFATKASPTGVILDLWEALQDDGDLNS	SASALEEMGKSEMLVANATDGDG	933
	Q9D398	CNSLDAPNSRGNDWRMLAQKLSMDRYLNYFATKASPTGVILDLWEALQDDGDLNS	SASALEEMGKSEMLVANATDGDG	945
	008722	CNSLDAPNSRGNDWRMLAQKLSMDRYLNYFATKASPTGVILDLWEALQDDGDLNS	SASALEEMGKSEMLVANATDGDG	945
	008747	CNSLDAPNSRGNDWRMLAQKLSMDRYLNYFATKASPTGVILDLWEALQDDGDLNS	SASALEEMGKSEMLVANATDGDG	931
	095185	CNSLDAPNSRGNDWRMLAQKLSMDRYLNYFATKASPTGVILDLWEALQDDGDLNS	SASALEEMGKSEMLVANATDGDG	931

The presence of identifiable domains in NOV1, as well as all other NOVX proteins, was determined by searches using software algorithms such as PROSITE, DOMAIN, Blocks, Pfam, ProDomain, and Prints, and then determining the Interpro number by crossing the domain match (or numbers) using the Interpro website (<http://www.ebi.ac.uk/interpro>). DOMAIN results for NOV1 as disclosed in Tables 1G-1O, were collected from the Conserved Domain Database (CDD) with Reverse Position Specific BLAST analyses. This BLAST analysis software samples domains found in the Smart and Pfam collections. For Tables 1G-1O and all successive DOMAIN sequence alignments, fully conserved single residues are indicated by black shading or by the sign (!) and “strong” semi-conserved residues are indicated by grey shading or by the sign (+). The “strong” group of conserved amino acid residues may be any one of the following groups of amino acids: STA, NEQK, NHQK, NDEQ, QHRK, MILV, MILF, HY, FYW.

Table 1J. Domain Analysis of NOV1a

gnl|Smart|smart00209, TSP1, Thrombospondin type 1 repeats; Type 1 repeats in thrombospondin-1 bind and activate TGF-beta. (SEQ ID NO:88)
CD-Length = 51 residues, 100.0% aligned
Score = 62.4 bits (150), Expect = 1e-10

Query: 249 WSSWAEWSPCSNRCGRGWQKRTRCTNPAPLNGGAFCEGQAFQKTACTT-ICP 300
| |+||| || | | || | | || | | + | | ||
Sbjct: 1 WGEWSEWSPCSVTGGGVQTRTRCCNPPP--NGGGPCTGPDTEETRACNEQPCP 51

5

Table 1K. Domain Analysis of NOV1a

gnl|Smart|smart00209, TSP1, Thrombospondin type 1 repeats; Type 1 repeats in thrombospondin-1 bind and activate TGF-beta. (SEQ ID NO:88)
CD-Length = 51 residues, 98.0% aligned
Score = 49.3 bits (116), Expect = 1e-06

Query: 305 WTEWSKWSACSTECAH-WRSRECMAPPQNGGRDCSGTLLDSKNCTDGLC 353
| |||+|| | | ++| | || | |+| +++ | + |
Sbjct: 1 WGEWSEWSPCSVTGGGVQTRTRCCNPPPNGGGPCTGPDTEETRACNEQPC 50

10

Table 1L. Domain Analysis of NOV1a

gnl|Pfam|pfam00531, death, Death domain. (SEQ ID NO:89)
CD-Length = 83 residues, 98.8% aligned
Score = 57.4 bits (137), Expect = 4e-09

Query: 852 QKICNSLDAPNSRGNDWRMLAQKLSM-DRYLNYPATKA----SPTGVILDLWEALQQDDG 906
+++| || | | ||| ||+| + + ++ + ||| +||| | +
Sbjct: 1 RELCKLLDDP--LGRDWRRLARKLGLSEEEIDQIEHENPRLASPTYQLLDLWEQRGKNA 58
Query: 907 DLNSLASALEEMGKSEMLVAVATD 930
+ +| || +||+ + + + +
Sbjct: 59 TVGTLLEALRKMRDDAVELESA 82

15

Table 1M. Domain Analysis of NOV1a

gnl|Pfam|pfam00090, tsp_1, Thrombospondin type 1 domain. (SEQ ID NO:90)
CD-Length = 48 residues, 91.7% aligned
Score = 49.7 bits (117), Expect = 7e-07

Query: 250 SSWAEWSPCSNRCGRGWQKRTRCTNPAPLNGGAFCEGQAFQKTACT 296
| |+||| || |+| + | || +|| || | | | + ||
Sbjct: 1 SPWSEWSPCSVTGKGIRTRQRTCNSPA---GKGPCGDAQETEACM 44

20

Table 1N. Domain Analysis of NOV1a

gnl|Smart|smart00409, IG, Immunoglobulin (SEQ ID NO:91)
CD-Length = 86 residues, 100.0% aligned
Score = 48.9 bits (115), Expect = 1e-06

5

Query: 159 PLGKEVPLDHEVLLQCRPPEGVPVAEVEWLKNEVDVIDPTQDTNFLTIDHN--LIIRQA 215
| | | | | | | | | | | | | | + + | ++
Sbjct: 1 PPSVTVKEGESVTLSCAS-GNPPPTVTWYKQGGKL-LAESGRFSVSRSGNSTLTISNV 58
Query: 216 RLSDTANYTCVAKNIVAKRRSTTATVIVY 244
| + | | | | | | | | + |
Sbjct: 59 TPEDSGTYTCAATNSSGSASSGT-TLTVL 86

Table 1O. Domain Analysis of NOV1a

gnl|Smart|smart00408, IGc2, Immunoglobulin C-2 Type (SEQ ID NO:92)
CD-Length = 63 residues, 87.3% aligned
Score = 42.7 bits (99), Expect = 9e-05

10

Query: 170 VLLQCRPPEGVPVAEVEWLKNEVDVIDPTQDTNFLTIDHNLIIIRQARLSDTANYTCVAKN 229
| | | | | | | + | | + + ++ ++ | | + | | + | | | + |
Sbjct: 6 VTLTC-PASGDPVPNITWLKDGKPLPESR----VVASGSTLTIKNVSLEDSGLYTCVARN 60

15

Migration of neurons from proliferative zones to their functional sites is fundamental to the normal development of the central nervous system. Disruption of the mouse rostral cerebellar malformation mutation (rcm) gene, also called the Unc5h3 gene, resulted in a failure of tangentially migrating granule cells to recognize the rostral boundary of the cerebellum. In rcm-mutant mice, the cerebellum is smaller and has fewer folia than in wildtype, ectopic cerebellar cells are present in midbrain regions by 3 days after birth, and there are abnormalities in postnatal cerebellar-neuronal migration. Ackerman et al. (1997). Sequence analysis has revealed that the predicted rcm mouse protein is a transmembrane protein that contains 2 immunoglobulin (Ig)-like domains and 2 type I thrombospondin (THBS1) motifs in the extracellular region. Ig and THBS1 domains are also found in the extracellular region of the *C. elegans* UNC5 transmembrane protein, and the C-terminal 865-amino acid region of Rcm is 30% identical to UNC5. In addition, the UNC5 protein is essential for dorsal guidance of pioneer axons and for the movement of cells away from the netrin ligand. Ackerman et al. (1997). In the developing brain of vertebrates, netrin-1 plays a role in both cell migration and axonal guidance.

30

In the developing nervous system, migrating cells and axons are guided to their targets by cues in the extracellular environment. The netrins are a family of phylogenetically conserved guidance cues that can function as diffusible attractants and repellents for different classes of cells and axons. In vertebrates, insects and nematodes, members of the DCC

subfamily of the immunoglobulin superfamily have been implicated as receptors that are involved in migration towards netrin sources. In *Caenorhabditis elegans*, the transmembrane protein UNC-5 has been implicated in these responses, as loss of UNC-5 function causes migration defects and ectopic expression of UNC-5 in some neurons can redirect their axons away from a netrin source.

The disclosed NOV1 nucleic acid of the invention encoding a UNC5H2-like protein includes the nucleic acid whose sequence is provided in Table 1A, 1C or a fragment thereof. The invention also includes a mutant or variant nucleic acid any of whose bases may be changed from the corresponding base shown in Table 1A or 1C while still encoding a protein that maintains its UNC5H2 like activities and physiological functions, or a fragment of such a nucleic acid. The invention further includes nucleic acids whose sequences are complementary to those just described, including nucleic acid fragments that are complementary to any of the nucleic acids just described. The invention additionally includes nucleic acids or nucleic acid fragments, or complements thereto, whose structures include chemical modifications. Such modifications include, by way of nonlimiting example, modified bases, and nucleic acids whose sugar phosphate backbones are modified or derivatized. These modifications are carried out at least in part to enhance the chemical stability of the modified nucleic acid, such that they may be used, for example, as antisense binding nucleic acids in therapeutic applications in a subject. In the mutant or variant nucleic acids, and their complements, up to about 16 percent of the bases may be so changed.

The disclosed NOV1 protein of the invention includes the UNC5H2-like protein whose sequence is provided in Table 1B or 1D. The invention also includes a mutant or variant protein any of whose residues may be changed from the corresponding residue shown in Table 1B or 1D while still encoding a protein that maintains its UNC5H2-like activities and physiological functions, or a functional fragment thereof. In the mutant or variant protein, up to about 9 percent of the residues may be so changed.

The invention further encompasses antibodies and antibody fragments, such as F_{ab} or $(F_{ab})_2$, that bind immunospecifically to any of the proteins of the invention.

The above defined information for this invention suggests that this UNC5H2-like protein (NOV1) may function as a member of a “UNC5H2 family”. Therefore, the NOV1 nucleic acids and proteins identified here may be useful in potential therapeutic applications implicated in (but not limited to) various pathologies and disorders as indicated below. The potential therapeutic applications for this invention include, but are not limited to: protein therapeutic, small molecule drug target, antibody target (therapeutic, diagnostic, drug

targeting/cytotoxic antibody), diagnostic and/or prognostic marker, gene therapy (gene delivery/gene ablation), research tools, tissue regeneration *in vivo* and *in vitro* of all tissues and cell types composing (but not limited to) those defined here.

The NOV1 nucleic acids and proteins of the invention are useful in potential
5 therapeutic applications implicated in cancer including but not limited to various pathologies and disorders as indicated below. For example, a cDNA encoding the UNC5H2-like protein (NOV1) may be useful in gene therapy, and the UNC5H2-like protein (NOV1) may be useful when administered to a subject in need thereof. By way of nonlimiting example, the compositions of the present invention will have efficacy for treatment of patients suffering
10 from cardiomyopathy, atherosclerosis, hypertension, congenital heart defects, aortic stenosis, atrial septal defect (ASD), atrioventricular (A-V) canal defect, ductus arteriosus, pulmonary stenosis, subaortic stenosis, ventricular septal defect (VSD), valve diseases, tuberous sclerosis, scleroderma, obesity, transplantation, diabetes, autoimmune disease, renal artery stenosis, interstitial nephritis, glomerulonephritis, polycystic kidney disease, systemic lupus
15 erythematosus, renal tubular acidosis, IgA nephropathy, hypercalcaemia, Lesch-Nyhan syndrome, Von Hippel-Lindau (VHL) syndrome, Alzheimer's disease, stroke, tuberous sclerosis, Parkinson's disease, Huntington's disease, cerebral palsy, epilepsy, Lesch-Nyhan syndrome, multiple sclerosis, ataxia-telangiectasia, leukodystrophies, behavioral disorders, addiction, anxiety, pain, neuroprotection, cancers, and/or other pathologies and disorders. For
20 example, a cDNA encoding the transmembrane receptor UNC5H2-like protein may be useful in transmembrane receptor UNC5H2 therapy, and the transmembrane receptor UNC5H2-like protein may be useful when administered to a subject in need thereof. By way of nonlimiting example, the compositions of the present invention will have efficacy for treatment of patients suffering from cardiomyopathy, atherosclerosis, hypertension, congenital heart defects, aortic
25 stenosis, atrial septal defect (ASD), atrioventricular (A-V) canal defect, ductus arteriosus, pulmonary stenosis, subaortic stenosis, ventricular septal defect (VSD), valve diseases, tuberous sclerosis, scleroderma, obesity, transplantation, diabetes, autoimmune disease, renal artery stenosis, interstitial nephritis, glomerulonephritis, polycystic kidney disease, systemic lupus erythematosus, renal tubular acidosis, IgA nephropathy, hypercalcaemia, Lesch-Nyhan
30 syndrome, Von Hippel-Lindau (VHL) syndrome, Alzheimer's disease, stroke, tuberous sclerosis, Parkinson's disease, Huntington's disease, cerebral palsy, epilepsy, Lesch-Nyhan syndrome, multiple sclerosis, ataxia-telangiectasia, leukodystrophies, behavioral disorders, addiction, anxiety, pain, neuroprotection, cancers, and other diseases, disorders and conditions of the like. Also since this gene is expressed at a measurably higher level in several cancer

cell lines (including breast cancer, CNS cancer, colon cancer, gastric cancer, lung cancer, melanoma, ovarian cancer and pancreatic cancer), it may be useful in diagnosis and treatment of these cancers. The NOV1 nucleic acid encoding the UNC5H2-like protein of the invention, or fragments thereof, may further be useful in diagnostic applications, wherein the presence or amount of the nucleic acid or the protein are to be assessed.

NOV1 nucleic acids and polypeptides are further useful in the generation of antibodies that bind immuno-specifically to the novel NOV1 substances for use in therapeutic or diagnostic methods. These antibodies may be generated according to methods known in the art, using prediction from hydrophobicity charts, as described in the "Anti-NOVX Antibodies" section below. The disclosed NOV1 proteins have multiple hydrophilic regions, each of which can be used as an immunogen. In one embodiment, a contemplated NOV1 epitope is from about amino acids 1 to 100. In another embodiment, a NOV1 epitope is from about amino acids 200 to 300. In further embodiments, a NOV1 epitope is from about amino acids 450 to 500, from about amino acids 600 to 900, from about amino acids 950 to 1000, from about amino acids 1200 to 1300, from about amino acids 1400 to 1600, from about amino acids 1800 to 1900, from about amino acids 1950 to 2050, and from about amino acids 2200 to 2300. These novel proteins can be used in assay systems for functional analysis of various human disorders, which will help in understanding of pathology of the disease and development of new drug targets for various disorders.

NOV2

NOV2 includes three novel protein tyrosine phosphatase precursor-like proteins disclosed below. The disclosed sequences have been named NOV2a, NOV2b, and NOV2c.

NOV2a

A disclosed NOV2a nucleic acid of 6994 nucleotides (also referred to as SC126422078_A) encoding a receptor protein tyrosine phosphatase precursor-like protein is shown in Table 2A. An open reading frame was identified beginning with an ATG initiation codon at nucleotides 31-33 and ending with a TAA codon at nucleotides 6874-6876. A putative untranslated region upstream from the initiation codon and downstream from the termination codon is underlined in Table 2A. The start and stop codons are in bold letters.

Table 2A. NOV2a nucleotide sequence (SEQ ID NO:5).

TGATTCTACTGGCTGAAAAATGTAATAAAGATGGATTTTCTTATCATTTTCTTTTACTTTTTATTTGGGACT
 TCAGAGACACAGGTAGATGTTTCCAATGTCGTTCTCTGGTACTAGGTACGATATAACCATCTCTTCAATTTCT
 ACAACATACACCTCACCTGTTACTAGAATAGGGGCTTCTAATGAACCAGGGCTCCAGTCTTCTAGCCGGG
 GAAAGAGTCGGATCTGCTGGGATTCTTCTGTCTTGAATACACCACCTAATCCAAATGGAAGGATTATATCT
 TACATTGTCAAATATAAGGAAGTTTGTCCGTGGATGCAAACAGTATATACAAAGTCAGATCAAAGCCAGAC
 AGTCTGGAAGTTCTTCTTACTAATCTTAATCTTGAACAACATATGAAATTAAGGTAGCTGCTGAAACAGT
 GCTGGCATTGGAGTGTTTAGTGATCCATTTCTCTTCCAACTGCAGAAAGTCTCCAGGAAAGTGGTGGAT
 TTCACAGGTGAGGCTGTCCCGTTCAGCAGTAAGCTGATGTGGTATACCTCGGCAACCAAAAAAATTACC
 AGCTTCAAGATTAGTGTCAGCATAAACAGAAGTGGGATAGTAGTGAAGAAGTGTCAATCAGAGTGGAGTGC
 ATTTTAAGTGCTTCCCTTCTTGTCACTGCAACGAGAATAGTGAATCTTTTTATGGAGTACAGCCAGCCCT
 TCTCCAACCTTGGTAGAGTTACACCTCCATCGCGTACCACATTCATCAAGCAGCTTGACACAGAATGAG
 ATCAGCTCTGTGAAAGAGCCTATCAGTTTGTAGTGACACACTTGAGACCTTATACAACATATCTTTTGAA
 GTTTTCAAGCTGCTCAAACTGAAGCAGGTTATATTGATAGTACGATTGTCAGAACACCAGAATCAGTGCCTGAA
 GGACCACCACAAAAGTGCCTAACAGGCAACATCAGGAAAGTCCCTTTCAATTTTATGGGACCCCAACT
 ATAGTAACAGGGAAATTTAGTTATAGAGTTGAATTATATGGACCATCAGCAGGTGCGATTTTGGATAACAGC
 ACAAAAGACCTCAAGTTTGCATTACCTAACCTAACACCATTTACAATGTATGATGTCTATATTGCGGTGAA
 ACCAGTGCAGGGACTGGGCCCAAGTCAAATATTTTCACTTACTCCACCAGATGTTCCAGGGGAGTGT
 GATTTACAACTTGAGAGGTAGAATCCACGCAAGTAAGAATTACTTGAAGAAGAACACGACAACCAAATGGA
 ATTATTAACCAATACCGAGTGAAAGTCTAGTTCCAGAGACAGGAATAATTTTGAAAAATCTTTTGCTCACT
 GGAAATAATGAGATAAATGACCCCATGGCTCCAGAAATTTGTGAACATAGTACAGCCAAATGGTAGGATTATAT
 GAGGGTTGAGCAGAGATGTCGTCTGACCTTCACTCACTTGCTACATTTATATATAACAGCCATCCAGATAAA
 AACTTTCTGCAAGGAATAGAGCTGAAGACCAGACTTCCACAGTTGTAACCTACAAGGAATCAGTATATTACT
 GACATTGCAAGCTGAACAGCTGACTTATGTTCTTATCAGATTAAGGAGATTTTGGGCTGAGCAATGGGGTTT
 TCTAGATATACAATCATGTCTATGCAAGCAGGACAATTTGACTTCCCAGGCTTTTGTCAAGCCCAAAAT
 TTCAGAGTTACACATGTTACCATAACAGAAGTATTTTTTCACTGGGATCCTCCAGATCCTGTATTTTTTTCAT
 CATACCTTATCACTATTTTGGATGTTGAAACCAATCCAAGAGTATTTTAAAGGACATTAACAGTTTGTG
 TCTCTTGCTCTTATAGGGTTAAAGAAATACAAAAATGAGAGTGGCAGCCTCAACCCAGTTGGA
 GAAAGTTCTTTGTCTGAAGAAATGACATCTTTGTGAGAACTTCAGAAAGTGAACCGGAATCATCACTCAA
 GATGTGCAAGTAATGATGTTACCGCAGATGAAATAAGGTTGAAGTGGTACCACCCGAAAGCCCAATGGG
 ATCATTATTGCTTATGAAGTGCTATATAAAAAATAGATACTTTTATATGAAGAACACATCAACACAGAC
 ATAATATTAAGGAACCTTAAGACCTCACCCCTTATAAATCTTCTGTAAGGCTTACACAGATTTGGTCAAT
 GGCAATCAGGTATCTTCTTACTCTCTGTAAGGACTTCGGAGTCAGTGCCTGATAGTGACCCAGAAAATATC
 ACTTACAAAAATATTTCTTCTGGAGAGATTGAGCTATCATTCCTTCCCCAAGTAGTCCCAATGGAATCATA
 CAAAAATATACAATTTATCTCAAGAGAAGTAATGGAATGAGGAAAGAACTATAAATACAACCTCTTTAACC
 CAAAAATTAAGGCTGTAAGAAATATACCCAATATATCATTGAGGTGCTGCTAGTACATCAAGGTTGAA
 GGAGTTCGGAGTGCTCCCATAGTATACTGACGGAGGAAGATGCTCCTGATTCTCCCCCTCAAGACTTCTCT
 GTAAACAGTTGTCTGGTGTCAGGTGAAGTTGTCTGCAACCAACCCCTGGAGCCAAATGGAATTATCTCT
 TATTACACAGTTTATGCTGAGATCATTAATAAATCTTAAATGTCACTGAAACATCATTTGGAGTTATCA
 GATTTGGATTATAATGTTGAATACAGTGCTTATGTAACAGCTAGCACCAGATTTGGTATGGGAAAAAAGA
 AGCAATATCATTAGCTTTCAAACACCAGAGGGACCAAGCGATCCTCCCAAGATGTTTATTATGCAACCTC
 AGTCTCTCATCAATAATCTTTTCTGGACACCTCCTTCAAAACCTAATGGGATTATACAATATTACTCTGTT
 TATTACAGAAATCTTCAAGTACTTTTATGCAAGATTTTACACTCCATGAAGTAACCAATGACTTTGACAA
 ATGACTGTATCCACAATTATAGATAAAGTGAATATTCAGTACTATACATTTTGGTTAAACAGCAAGTACT
 TCAGTTGAAATGGGAATAAAGCAGTGACATCATTGAAGTATACACAGATCAAGACGTACCTGAAGGGTTT
 GTTGGAAACCTGACTTACGAATCCATTTCTGCAACTGCAATAAATGTAAGCTGGGTCCCACCGGCTCAACCA
 AACGCTCTAGTCTTCTACTATGTTTCACTGATCTTACAGCAGACTCCTCGCCATGTGAGACCACTCTTGT
 ACATATGAGAGAAGCATATATTTGATAATCTGAAAAATACACTGATTATATATTAATAAATTACTCCATCA
 ACAGAAAAGGGATTCTCTGATACCTATCTGCCAGCTATACATCAAGACTGAAGAAGATATCCAGAAACT
 TCACCAATAATCAACACTTTTAAAAACCTTCTCTACCTCAGTTCTCTTATCATGGGATCCCCAGTAAAG
 CCAATATGGTGCAATAAATAGTTATGATTTAACTTTACAAGGACCAATGAAATTTATCTTCTTACTTCT
 GATAATTACATAATATTGGAAGAGCTTTCACCATTTACATTTATAGCTTTTTTGTGCTGCGCAAGAACTAGA
 AAAGGACTTGGTCTTCCAGTATTCTTTCTTTTACACAGATGAGTCAGTGCCTTAGCACCTCCACAAAT
 GTTAAAGTATATAGTTTAAATTCATGAACATGAAACTGACACTATATATTATAAGAATATATCAGGATTT
 AAAACTGAAGCCAACTTGTGGAGTGAACAGTCAGCACTACTCTATCCGTGTATCTGCGTTACACAAA
 GTTGGAAATGGCAATCAATTTAGTAATGTAGTAAATTCACAACCAAGAATCAGTTCCAGATGTCGTGCAG
 AATATGCAAGTGCATGGCACTAGCTGGCAGTCAGTTTGTAGTAAATGGGATCCACCCAAAAGGCAATGGA
 ATAATAACGCAGTATATGGTAACAGTTGAAAGGAATCTACAAAAGTTTCTCCCAAGATCACATGTACACT
 TTCATAAAGCTTCTTGCCAATACCTCATATGTCTTTAAAGTAAGAGCTTCAACCTCAGCTGGTGAAGGTGAT
 GAAAGCACATGCCATGTGACACACTACCTGAAACAGTTCCTCAGTGTCCCAAAAATATTGCTTTTCTGAT
 GTTCAGTCAACTAGTGCAACATTGACATGGATAAGACCTGACACTATCCTTGGCTACTTTCAAATTCACAA
 ATTACCACTCACTTCGTGCTCAAAAATGCAAGAATGGGAATCCGAAGAATGTGTTGAATATCAAAAAATT
 CAATACCTCTATGAAGCTCACTTAACTGAAGAGACAGTATATGGATTAAAGAAATTTAGATGGTATAGATT
 CCAAGTGGCTGCCAGCAACATGCTGGCTATGGCAATGCTTCAAACTGGATTTCTACAAAACTCTGCTGGC
 CCTCCAGATGGTCTCTGAAATGTTCTAGTAGCAACATCACTTTTAGCATCAGCATCAAGCTGGAGT
 GAACCTGCTGTCATTACTGGACCAACATGTTATCTGATTGATGTCAAATCGGTAGATAATGATGAATTTAAT
 ATATCTTCATCAAGTCAATGAAGAAAATAAAACCATAGAAATTAAGATTAGAAATATTCACAAGGTAT

TCTGTAGTGATCACTGCATTTACTGGGAACATTAGTGCTGCATATGTAGAAGGGAAGTCAAGTGCTGAAATG
ATTGTTTACTACTTTAGAATCAGCCCCAAAGGACCCACCTAACACATGACATTTTCAAGAGATACCAGATGAA
GTTACAAAATTTCAATTAACGTTCCCTCCTCTCTCAACCTAATGGAAATATCCAAGTATATCAAGCTCTG
GTTTACCGAGAAGATGATCCTACTGCTGTCCAGATTCAACACCTCAGTATTATACAGAAAACCAACACATTC
GTCATTGCAATGCTAGAAGGACTAAAAGGTGGACATACATACAATATCAGTGTTCACGAGTCAATAGTGCT
GGTGCAAGTCCAAAGGTTCCGATGAGAATAACCATGGATATCAAAGCTCCAGCAGACCAAAAACCAACCA
ACCCCTATTTATGATGCCACAGGAAAACCTGCTGTGACTTCAACAACAATTACAATCAGAATGCCAATATGT
TACTACAGTGATGATCATGGACCAATAAAAAATGTACAAGTGCTTGTGACAGAAACAGGAGCTCAGCATGAT
GGAAATGTAACAAAGTGGTATGATGCATATTTTAATAAAGCAAGGCCATATTTTACAAATGAAGGCTTTCCCT
AACCTTCCATGTACAGAAGGAAAGACAAAGTTTAGTGGCAATGAAGAAATCTACATCATAGGTGCTGATAAT
GCATGCATGATTCTTGGCAATGAAGACAAAATTTGCAATGGACCACTGAAACCAAAAAGCAATACTTATTT
AAATTTAGAGCTACAAATATTATGGGACAATTTACTGACTCTGATTATTTGACCTGTTAAGACTTTAGGC
GAAGGACTTTTCAAGAAAGAACCGTAGAGATCATTTCTTCCGTCACTTTGTGTATCCTTTCAATAATTCTCCT
GGAACAGCTATTTTGCATTTGCAAGAATTCGACAGAAGCAGAAAGAAGGTGGCACATACTCTCCTCAGGAT
GCAGAAATATTGACACTAAATTGAAGCTGGATCAGCTCATCAGTGGCAGACCTGGAAGTGAAGGACGAG
AGATTTACGCGGCCAATAAGCAAGAAATCCTTCTGCAACATGTTGAAGAGCTTTGCAACAACCAACACTA
AAGTTTCAAGAAAGAAATTTTCGGAATTACCAAAATTTCTTCAAGATCTTTCTTCAACTGATGCTGATCTGCCT
TGAATAGAGCAAAAACCGCTTCCCAAAACATAAAACCATATAATAAACAAGAGTAAAGCTGATAGCTGAC
GCTAGTGTTCAGGTTTCGGATTATATTAATGCCAGCTATATTTCTGGTTATTTATGTCCAAATGAATTTATT
GGTGTTCAGGTTCCACTACAGGAACAGTTGGAGATTTTGGAGAATGGTGTGGGAAACAGAGCAAAAACA
TTAGTAATGCTAACACAGTGTTTTGAAAAAGGACGGATCAGATGCCATCAGTATTGGCCAGAGGACAACAAG
CCAGTTACTGTCTTTGGAGATATAGTGATTACAAAGCTAATGGAGGATGTTCAAATAGATTGGACTATCAGG
GATCTGAAAATTGAAAGGCATGGGGATTGCATGACTGTTGCAGAGTGAACCTTTACTGCCTGGCCAGAGCAT
GGGGTTCCCTGAGAACAGCGCCCTCTAATTCATTTGTGAAGTTGGTTCGAGCAAGCAGGGCATGACACC
ACACCTATGATTGTTCACTGCAGTGCTGGAGTTGGAAGAACTGGAGTTTTTATTGCTCTGGACCATTAAACA
CAACATATAAATGACCATGATTTTGTGGATATATAGGACTAGTAGCTGAACTGAGAAGTGAAAGAATGTGC
ATGGTGCAGAATCTGGCACAGTATATCTTTTACACAGTGCACTCTGGATCTCTTATCAAATAAGGGAAGT
AATCAGCCCATCTGTTTTGTAACTATTCAGCACTTCAGAAGATGACTCTTTGGACGCCATGGAAGGTGGT
GATGTTGAGCTTGAATGGGAAGAAACCACTATGTAATAATTCAGACCAAGGATACAATTGGAAGAGATTTT
TAAATCCAGGGGCCAAAGTTACCCCTCATTTCTCGAATTGAAATGTGCACCTTAAAGAAATATCTATG
CTTCTCTCAC

In a search of public sequence databases, the NOV2a nucleic acid sequence, located on chromosome 12 has 777 of 3293 bases (84%) identical to a gb:GENBANK-
ID:AF063249|acc:AF063249.1 mRNA from *Rattus norvegicus* (*Rattus norvegicus* glomerular
mesangial cell receptor protein-tyrosine phosphatase precursor (PTPRQ) mRNA, complete
5 cds) (E = 0.0). Public nucleotide databases include all GenBank databases and the GeneSeq
patent database.

The disclosed NOV2a polypeptide (SEQ ID NO:6) encoded by SEQ ID NO:5 has 2281
amino acid residues and is presented in Table 2B using the one-letter amino acid code. Signal
10 P, Psort and/or Hydropathy results predict that NOV2a has a signal peptide and is likely to be
localized in the plasma membrane with a certainty of 0.4600. In other embodiments, NOV2a
may also be localized to the microbody (peroxisome) with a certainty of 0.1381, the
endoplasmic reticulum (membrane) with a certainty of 0.1000 or in the endoplasmic reticulum
(lumen) with a certainty of 0.1000. The most likely cleavage site for a NOV2a peptide is
15 between amino acids 17 and 18, at: SET-QV.

Table 2B. Encoded NOV2a protein sequence (SEQ ID NO:6).

MDFLIIIFLLFIGTSETQVDVSNVVPTRYDITISSISTYTSVPVTRIGASNEPFPVFLAGERVGSAGILL
SWNTPPNPNGRIISYIVKYKEVCPWMQTVYTQVRSKPDSLEVLLTNLNPQTYYEIKVAENASAGIGVFSDFP
LFQTAESAPGKVVDFTGEAVPFSSKLMWYTSATKKKITSFKISVKHNRSGIVVKEVSIRVECILSASLPLHC

NENSESFLWSTASPSPTLGRVTPPSRTTHSSSTLTQNEISSVKEPISFVTHLRPYTTYLFVSAATTEAGY
IDSTIVRTPESVPEGPPQNCVTGNITGKSFSILWDPPTIVTGKFSYRVELYGPSAGRILDNSTKDLKFAFTN
LTPFTMYDVYIAAETSAGTGPKSNISVFTPPDVPDGLQAEVESTQVRITWKKPRQNGIINQYRVKVL
VPETGIIILENTLLTGNNEINDPMAPEIVNIVQPMVGLYEGSAEMSSDLHSLATFIYNHPDKNFPPARNRAED
QTSPVVTTNRQYITDIAAEQLTYVLIRLRFFWAETMGFSRYTIMSSASRDNLTPGPLSAQNFRVTHVTITE
VFLHWDPPDPVFFHHYLITILDVENQSKSIILRLNLSLVLIGLKKYTKYKMRVAASTHVGESSLSEENDI
FVRTSEDEPESSPDVEVIDVTADIEIRLKWSPPEKPNGIIAYEVLYKNIDTLYMKNTSTTDIILRNLRPHT
LYNISVRSYTRFGHGNQVSSLLSVRTSESVSDAPENITYKNISSGEIELSFLPPSSPNGIIQKYTIYLRKS
NGNEERTINTTSLTQNIKGLKKYQYIIIEVSASTLKGEVRSAPISILTEEDAPDPPQDFSVKQLSGVTVK
LSWQPPLEPNGIILYTVYVWRSSSLKTINVTETSLSDLDYNVEYSAYVTASTRFGDGKTRSNIIISFQTPE
GPSDPPKDVYANLSSSSIIILFWTPPSKPNGIIQYYSVYRYNTSGTFMQNFTLHEVTNDFDNMTVSTIIDKL
TIFSYITFWLTASTSVGNNGKSSDIEVYTDQDVPEGFVGNLTYESISSTAINVSWVPPAQPNGLVFYVYVSL
ILQOTPRHVRPPLVYERSIYFDNLEKYTDYILKITPSTKEGFSPTYAQLYIKTEEDIPETSPIINTFKNL
SSTSVLLSWDPPVKPNGAIIISYDLTLQGNENYSFITSNDYIILEELSPFTLYSFFAAARTKGLGPSSILF
FYTDESVPPLAPPQNLTINCTSDFVWLKWSPPPLPGGIVKVYSFKIHEHETDTIYKNSIGFKTEAKLVGLE
PVSTYSIRVSAFTKVGNGNQFSNVVKFTQESVDPDVQNMQCMATSWQSVLVKWDPPKKANGIITQYMTVE
RNSTKVPQDHMYTFIKLLANTS YVFKVRASTSAGEDESTCHVSTLPETVPSVPTNIAFSDVQSTSATLTW
IRPDTILGYFQNYKITTLQRAQCKEWESEECVEYQKIQLYEAHLTEETVYGLKKFRWYRFQVAASTNAGY
GNASNWISTKTLPGPPDGPENHVHVSATSPFSISISWSEPAVITGPTCYLIDVKSVDNDEFNISFIKSNEEN
KTIEIKDLEIFTRYSVVITAFGTGNISAAVEGKSSAEMIVTTLESAPKDPNNMTFQKIPDEVTKFQLTFLP
PSQPNNGNIQVYQALVYREDDPTAVQIHNLISIIQKTNTFVIAMLEGLKGGHTYNIISVYAVNSAGAGKVPMRI
TMDIKAPARPKTKPTPIYDATGKLLVTSTTITIRMPICYSDDHGPIKNVQVLVTETGAQHDGNTWKYDAY
FNKARPYFTNEGFPNPPCTEGKTKFSGNEEIIYIGADNACMIPGNEDKICNGPLKPKKQYLFKFRATNIMGQ
FTDSDYSDPVKTLGEGLSERTVEIILSVTLCLISIIILLGTAFIFARIRQKQKEGGTYSPODAEIIDTKLKL
DQLITVADLELKDRLTRPISSKSFLOHVEELCTNNNLKFOEEFSELPKFLQDLSSTDADLPWNRAKNRFPN
IKPYNNNRVKLIADASVPGSDYINASYISGYLCPNEFIATQGPLPGTVGDFWRMVWETRAKTLVMLTQCCEK
GRIRCHQWPEDNKPVTVFGDIVITKLMDVQIDWTIRDLKIERHGDCMTVRQCNTAWPEHGVPENSAPLI
HFVKLVASRAHDTTPMIVHCSAGVGRGTGVFIADHLTQHINDHDFVDIYGLVAELRSERMCMVQNLAQYIF
LHQCILDLLSNKGSNQPICFVNYALQKMSDLDAMEGGDVELEWEETM

A search of sequence databases reveals that the NOV2a amino acid sequence has 1894
of 2301 amino acid residues (82%) identical to, and 2078 of 2301 amino acid residues (90%)
similar to, the 2302 amino acid residue ptnr:SPTREMBL-ACC:O88488 protein from *Rattus*
5 *norvegicus* (Rat) (Glomerular Mesangial Cell Receptor Protein-Tyrosine Phosphatase
Precursor (EC 3.1.3.48)) (E = 0.0). Public amino acid databases include the GenBank
databases, SwissProt, PDB and PIR.

NOV2 is expressed in at least kidney and colon. This information was derived by
determining the tissue sources of the sequences that were included in the invention including
10 but not limited to SeqCalling sources, Public EST sources, Literature sources, and/or RACE
sources.

In addition, the sequence is predicted to be expressed in *Rattus norvegicus* :kidney
because of the expression pattern of (GENBANK-ID: gb:GENBANK-
ID:AF063249|acc:AF063249.1) a closely related *Rattus norvegicus* glomerular mesangial cell
15 receptor protein-tyrosine phosphatase precursor (PTPRQ) mRNA, complete cds homolog.

NOV2b

A disclosed NOV2b nucleic acid of 2565 nucleotides (also referred to as CG50718-02)
encoding a novel Glomerular Mesangial Cell Receptor Protein-Tyrosine-like protein is shown
20 in Table 2C. An open reading frame was identified beginning with an AGA codon at

nucleotides 1-3 and ending with a GAG codon at nucleotides 2563-2565. The start and stop codons are in bold letters in Table 2C. Because the first and last codons are not traditional initiation and termination codons, NOV2b could represent a partial reading frame that extends in the 5' and/or 3' directions.

5

Table 2C. NOV2b nucleotide sequence (SEQ ID NO:7).

AGATCTCCTGAAGGGTTTGGTGGAAACCTGACTTACGAATCCATTTCGTCAACTGCAATAAATGTAAGCTGG
GTCCACCGGCTCAACCAACGGTCTAGTCTTCTACTATGTTCCTGATCTTACAGCAGACTCCTCGCCAT
GTGAGACCACCTCTGTACATATGAGAGAAGCATATATTTGATAATCTGGAAAAATACACTGATTATATA
TTAAAAATTACTCCATCAACAGAAAAGGGATTCTCTGATACCTATACTGCCAGCTATACATCAAGACTGAA
GAAGATGTCAGAAAACCTTACCAATAATCAACACTTTTAAAAACCTTCTCTACCTCAGTTCTCTTATCA
TGGGATCCCCAGTAAAGCCAAATGGTGCAATAATAAGTTATGATTAACTTTACAAGGACCAATGAAAAAT
TATTCTTTCATTACTTCTGATAATTACATAATATTGGAAGAGCTTTCACCATTACATTATATAGCTTTTTT
GCTGCCGCAAGAACTAGAAAAGGACTTGGTCCCTCCAGTATTCTTTCTTTTACACAGATGAGTCAGTGCCG
TTAGCACCTCCACAAAATTGACTTTAATCAACTGTACTTCAGACTTTGTATGGCTGAAATGGAGCCCAAGT
CCTCTTCCAGGTGGTATTGTTAAAGTATATAGTTTAAAAATTTCATGAACATGAAACTGACACTATATATTAT
AAGAATATATCAGGATTTAAACTGGAAGCCAACTTGTGGACTGGAACAGTCAGCACCTACTCTATCCGT
GTATCTGCGTTCCACAAAGTTGGAATGGCAATCAATTTAGTAATGTAGTAAATTCACAAACCAAGAATCA
GTTCCAGATGCTGTCAGAAATATGCAGTGCATGGCAACTAGCTGGCAGTCAGTTTGTAGTAAATGGGATCCA
CCCAAAAGGCAATGGAATAATAACGCAGTATATGGTAACAGTTGAAAGGAATTCACAAAAGTTTCTCCC
CAAGATCACATGTACACTTTCATAAAGCTTCTTGCCAAATACCTCATATGTCTTTAAAGTAAGAGCTTCAACC
TCAGCTGGTGAAGGTGATGAAAGCACATGCCATGTCAGCACACTACCTGAAACAGTTCCAGTGTTCACACA
AATATTGCTTTTTCTGATGTTTCACTCACTAGTGCAACATTGACATGGATAAGACCTGACACTATCCTTGGC
TACTTTCAAATTACAAAATTACCACTCAACTTCGTGCTCAAAAATGCAAGAATGGGAATCCGAAGAATGT
GTTGAATATCAAAAAATCAATACCTCTATGAAGCTCACTTAACTGAAGAGACAGTATATGGATTAAGAAA
TTTAGATGGTATAGATTCCAAGTGGCTGCCAGCACCAATGTCTGGCTATGGCAATGCTTCAAACCTGGATTCT
ACAAAACCTCTGCTGGCCCTCCAGATGGTCTCTCTGAAAATGTTTCATGTAGTAGCAACATCACCTTTTAGC
ATCAGCATAAGCTGGAGTGAACCTGCTGTCATTACTGGACCAACATGTTATCTGATTGATGTCAAATCGGTA
GATAATGATGAATTTAATATATCCTTCATCAAGTCAATGAAGAAAATAAAACCATAGAAATTAAGATTTA
GAAATATTCACAAAGGTATTCTGTAGTGATCACTGCACTTACTGGGAACATTAGTGCTGCATATGTAGAAGGG
AAGTCAAGTGTGAAATGATTGTTACTACTTTAGAATCAGCCCCAAAGGACCACTTAAACATGACATTT
CAGAAGATACAGATGAAGTTACAAAATTTCAATTAACGTCCCTTCTCTCTCAACCTAATGGAAATATC
CAAGTATATCAAGCTCTGGTTTACCGAGAAGATGATCCTACTGCTGTCCAGATTCAACCTCAGTATTATA
CAGAAAACCAACACATTTCGTCAATGCTAGAAGGACTAAAAGGTGGACATACATACAATATCAGTGTT
TACGAGTCAATAGTGCTGGTGCAGGTCCAAAGGTTCCGATGAGAATAACCATGGATATCAAAGCTCCAGCA
CGACCAAAAACCAACCAACCCCTATTTATGATGCCACAGGAAAACCTGCTGTGACTTCAACCAACAAATTACA
ATCAGAAATGCCAATATGTTACTACAGTGATGATCATGGACCAATAAAAAATGTACAAGTGCTTGTGACAGAA
ACAGGAGCTCAGCATGATGGAAATGTAACAAAGTGGTATGATGCATATTTAATAAAGCAAGCCATATTTT
ACAAATGAAGGCTTTCCTAACCTCCATGTACAGAAGGAAAGCAAAGTTTGTGGCAATGAAGAAATCTAC
ATCATAGGTGCTGATAATGCATGCATGATTCCTGGCAATGAAGACAAAATTTGCAATGGACCACTGAAACCA
AAAAAGCAATACCTTATTAAATTTAGAGCTACAAATATTATGGGCAAAATTTACTGACTCTGATTATTCTGAC
CCTGTTAAGACTTTAGGCGAAGGACTTTCAGAAAGAACCCTCGAG

The disclosed NOV2b polypeptide (SEQ ID NO:8) encoded by SEQ ID NO:7 has 855 amino acid residues and is presented in Table 2D using the one-letter amino acid code.

Table 2D. Encoded NOV2b protein sequence (SEQ ID NO:8).

RSPEGFVGNLTYESISSAINVSWVPPAQPNGLVFVYVSLILQQTTPRHVRPPLVTYERSIYFDNLEKYTDYI
LKITPSTEGFSDTYTAQLYIKTEEDVPETSPPIINTFKNLSSTSVLLSWDPPVKPNGAIIISYDLTLQGPEN
YSFITSDNYIIIEELSPTFLYSFFAAARTKGLGPSSILFFYTDESVPPLAPPQNLTINCTSDFWLKWSPS
PLPGGIVKVYSFKIHEHETDTIYKINISGPKTEAKLVGLEPVSTYSIRVSAFTKVGNNGNQPNSNVKFTQES
VPDVQNMQCMATSWQSVLVKWDPPKKANGIIITQYMTVERNSTKVSPODHMYTFIKLLANTSIVFKVRAST
SAGEGDESTCHVSTLPETVPSVPTNIAFSDVQSTSATLTWIRPDTILGYFQNYKITTLRLAQKCKEWESEEC
VEYQKIQLYEHLTEETVYGLKFRWYRFQVAASTNAGYGNASNWI STKTLPGPPDGPENHVHVVATSPFS
ISISWSEPAVITGPTCYLIDVKSVDNDEFNISIFIKSNEENKTIKIDLEIFTRYSVVITAFGTGNISAAAYVEG
KSSAEMIVTTLESAPKDPNNMTFQKIPDEVTKFQLTSLPPSQPNIGNIQVYQALVYREDDPTAVQIHNLSTII
QKNTFTVIAMLEGLKGGHTYNISVYAVNSAGAGPKVPMRITMDIKAPARPKTKPTPIYDATGKLLVTSTTIT

IRMPICYSDDHGPIKNVQVLVTETGAQHDGNVTKWYDAYFNKARPYFTNEGFPNPPCTEGKTKFSGNEEII
IIGADNACMI PGNEDKICNGPLKPKKQYLFKFRATNIMGQFTDSDYSDPVKTLGEGLSERTLE

NOV2b is expressed in Brain, Colon, Fetal brain, Germ Cell, Heart, Kidney, Prostate, Uterus, brain, breast, colon, kidney, lung.

5 NOV2c

A disclosed NOV2c nucleic acid of 6903 nucleotides (also referred to as CG50718-05) encoding a novel Glomerular Mesangial Cell Receptor Protein-Tyrosine Phosphatase Precursor-like protein is shown in Table 2E. An open reading frame was identified beginning with an ATG initiation codon at nucleotides 1-3 and ending with a TGA codon at nucleotides 10 6901-6903. A putative untranslated regions upstream from the initiation codon and downstream of the termination codon are underlined in Table 2E. The start and stop codons are in bold letters.

Table 2E. NOV2c nucleotide sequence (SEQ ID NO:9).

ATGGATTTCTTATCATTTTTCTTTTACTTTTATTGGGACTTCAGAGACACAGGTAGATGTTTCCAATGTC
GTTCTGGTACTAGGTACGATATAACCATCTCTCAATTTCTACAAATACACCTCACCTGTTACTAGAATA
GTGACAAACAAATGTAACAGAACAGGGCCTCCAGTCTTCTAGCCGGGAAAGAGTCGGATTCTGCTGGGATT
CTTCTGTCTTGGAAATACACCACCTAATCCAAATGGAAGGATTATATCTTACATTGTCAAATATAAGGAAGTT
TGTCCGTGGATGCAAACAGTATATACACAAGTCAGATCAAAGCCAGACAGTCTGGAAGTTCTTCTTACTAAT
CTTAATCCTGGAACAACATATGAAATTAAGGTAGCTGCTGAAAACAGTGTGGCATTGGAGTGTGTTAGTGAT
CCATTTCTCTTCCAACTGCAGAAAGTCCAGCTCCAGGAAAAGTGGTGAATCTCACAGTTGAGGCCTACAAC
GCTTCAGCAGTTAAGCTGATTTGGTATTTACCTCGGCAACCAATGGCAAAATTACCAGCTTCAAGATTAGT
GTCAAGCATGCCAGAAGTGGGATAGTAGTGAAAGATGTCTCAATCAGAGTAGAGGACATTTTACTGGGAAA
TTGCCAGAATGCAATGTAGAGAATAGTGAATCTTTTATGGAGTACAGCCAGCCCTTCTCCAACCTTGGT
AGAGTTACACCTCCATCGGTACCAACATTCATCAAGCACGTTGACACAGAATGAGATCAGCTCTGTGTGG
AAAGAGCCTATCAGTTTGTAGTGACACACTTGAGACCTTATACAACATATCTTTTGAAGTTTCAGCTGCT
ACAACCTGAAGCAGGTTATATTGATAGTACGATTGTGAGAACACCAAGTCAAGTGCCTGAAGGACCACCAAA
AACTGCGTAACAGGCAACATCACAGGAAAGTCTTTTCAATTTTATGGGACCCACCAACTATAGTAACAGGG
AAATTTAGTTATAGAGTTGAATTATATGGACCATCAGGTGCGATTTTGGATAACAGCACAAAAGACCTCAAG
TTTGCAATCACTAACCTAACACCATTTACATGTATGATGTCTATATTGCGGCTGAAACAGTGCAGGGACT
GGGCCAAGTCAAATATTTAGTATTTCACTCCACCAGATGTTCCAGGGGAGTGTGTTGATTTACAACCTTGCA
GAGGTAGAATCCACGCAAGTAAGAATTACTTGGAAAGAAACACGACAAACCAATGGAATTTATTAACCAATAC
CGAGTGAAAGTGCTAGTTCCAGAGACAGGAATAATTTGGAAAATACTTTGCTCACTGGAATAATGAGATA
AATGACCCCATGGCTCCAGAAATTGTGAACATAGTAGGCCAATGGTAGGATTATATGAGGGTTCAGCAGAG
ATGTCGTCTGACCTTCACTCACTTGCTACATTTATATATAACAGCCATCCAGATAAAACCTTCTGCAAGG
AATAGAGCTGAAGACCAGACTTCACCAAGTTGTAACATAAGGAATCAGTATATTACTGACATTGCAGCTGAA
CAGCTGTCTTATGTTATCAGGAGACTTGACCTTTCACTGAGCACATGATTAGTGTATCTGCTTTCACCATC
ATGGGAGAAGGACCACCAACAGTTCTCAGTGTAGGACACGTGAGCAAGTGCCAAAGCTCCATTAAATTTATA
AACTATAAAATATTAGTTCTTCTATCTATTTGTTATATTGGGATCCTCCAGAATATCCCAATGGAAAAATA
ACTCATATACGATTTTATGCAATGGAATTGGATACAAACAGAGCATTCCAGATAACTACCATAGATAACAGC
TTTCTCATAACAGGTATAGGGTTAAAGAAATACACAAAATACAAAATGAGAGTGGCAGCCTCAACCCACGTT
GGAGAAAGTTCTTTGTCTGAAGAAATGACATCTTTGTGAGAACTTCAGAAGATGAACCGGAATCATCACT
CAAGATGTGCAAGTAATTGATGTTACCGCAGATGAAATAAGGTTGAAGTGCTCACCAACCCGAAAAGCCCAAT
GGGATCATTATTGCTTATGAAGTGCTATATAAAATATAGATACCTTTATATATGAAGAACACATCAACAA
GACATAATATTAAAGAACTTAAGACCTCACACCTCTATAACATTTCTGTAAGGTTTACACCAGATTGTT
CATGGCAATCAGGTATCTTCTTACTCTCTGTAAGGACTTCGGAGACTGTGCCTGATAGTGACACAGAAAAT
ATCACTTACAAAATATTTCTTCTGGAGAGATTGAGCTATCATCTCTCCCAAGTAGTCCCAATGGAATC
ATACAAAATATACAATTTATCTCAAGAGAAGTAATGGAATGAGGAAAGAACTATAAATACAACCTCTTTA
ACCCAAAACATTCTGAAGAAATATACCCATATATCATTGAGGTGTCTGCTAGTACACTCAAGGTGAAGGA
GTTCCGAGTGCTCCATAAGTATACTGACGGAGGAAGATGCTCCTGATTCTCCCCCTCAAGACTTCTCTGTA
AAACAGTTGCTGTTGTGTCACGGTGAAGTTGTGTCAGCAACCAACCCCTGGAGCCAAATGGAATTTATCTTTAT
TACACAGTTTATGTCTGGAGGAATAGATCATATTAATAAATATTAATGTCACTGAAACATCATTGGAGTTA

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TCAGATTGGATTATAATGTTGAATACAGTGCTTATGTAACAGCTAGCACCAGATTGGTGATGGGAAAACA
AGAAGCAATATCATTAGCTTCAAACACCAGAGGGACCAAGCGATCCTCCCAAAGATGTTTATTATGCAAAAC
CTCAGTTCCTCATCAATAATCTTTCTGGACACCTCCTTCAAACCTAATGGGATTATACAATATTACTCT
GTTTATTACAGAAATACTTCAGGTACTTTTATGCAGAAATTTACACTCCATGAAGTAACCAATGACTTTGAC
AATATGACTGTATCCACAATTATAGATAAACTGACAATATTCAGCTACTATACATTTTGGTTAACAGCAAGT
ACTTCAGTTGGAAAATGGGAAATAAAGCAGTGACATCATTGAAGTATACACAGATCAAGACGTCCTGGAAGGG
TTTGTGGAAAACCTGACTTACGAATCCATTTTCGTCAACTGCAATAAATGTAAGCTGGGTCCCACCGGCTCAA
CCAAACGGTCTAGTCTTCTACTATGTTTCACTGATCTTACAGCAGACTCCTCGCCATGTGAGACCACCTCT
GTTACATATGAGAGAAGCATATATTTTGATAATCTGGAAAAATACACTGATTATATATTAATAAATTACTCCA
TCAACAGAAAAGGGATTCTCTGATACCTATACCTGCCCAGCTATACATCAAGACTGAAGAAGATGTCCCAGAA
ACTTCACCAATAATCAACACTTTTAAAAACCTTCTCTACCTCAGTTCTCTTATCATGGGATCCCCAGTA
AAGCCAAATGGTGCAATAATAAGTTATGATTTAACTTTACAAGGACCAATGAAAAATTATCTTTTCAATTACT
TCGATAATTACATAATATTGGAAGAGCTTTTACCATTATACATTATATAGCTTTTTTGTGCGCGAAGAAGT
AGAAAAGGACTTGGTCTTCCAGTATTCTTTTCTTTTACAGATGAGTCAGTGCCGTTAGCACCTCCACAA
AATTTGACTTTAATCAACTGTACTTCAGACTTTGTATGGCTGAAATGGAGCCCAAGTCTCTTCCAGGTGAGT
ATTGTTAAAGTATATAGTTTTTAAATTCATGAACATGAAACTGACACTATATATTATAAGAATATATCAGGA
TTTAAAACTGAAGCAAACCTGTTGGACTGGAACCACTCAGCACCTACTCTATCCGTGTATCTGCGTTCACC
AAAGTTGGAAAATGGCAATCAATTTAGTAATGTAGTAAATTCACAACCAAGAATCAGTTCAGATGTCTGTG
CAGAATATGCAGTGCATGGCAACTAGCTGGCAGTCAGTTTGTAGTAAATGGGATCCACCCAAAAGGCAAAAT
GGAATAATAACGCAGTATATGGTAACAGTTGAAAGGAATTCACAAAAGTTTCTCCCAAGATCACATGTAC
ACTTTCATAAAGCTTCTTGCCAATACCTCATATGTCTTTAAAGTAAAGAGCTTCAACCTCAGCTGGTGAAGGT
GATGAAAGCACATGCCATGTACGACACTACCTGAAACAGTTCAGTGTTCACCAAAATTTGCTTTTTTCT
GATGTTTCACTCACTAGTGCAACATTGACATGGATAAGACCTGACACTATCTTGGCTATCTTCAAAATFAC
AAAATTACCACTCAACTTCGTGCTCAAAAATGCAAAGAATGGGAATCCGAAGAATGTGTTGAATATCAAAAA
ATTCAATACCTCTATGAAGCTCACTTAACTGAAGAGACAGTATATGGATTAAAGAAATTTAGATGGTATAGA
TTCCAAGTGGCTGCCAGCACCAATGTCTGGCTATGGCAATGCTTCAAACTGGATTCTTCAAAAACCTCTGCT
GGCCCTCCAGATGGTCTCTGAAAAATGTTTATGTAGTAGCAACATCACCTTTTAGCATCAGCATAAGCTGG
AGTGAACCTGCTGTCTATTACTGGACCAACATGTTATCTGATTGATGTCAAAATCGGTAGATAATGATGAATTT
AATATATCCTTCATCAAGTCAAATGAAGAAAATAAAACCATAGAAATTAAGATTAGAAAATATTCACAAGG
TATTCTGTAGTGATCACTGCAATTTACTGGGAACATTAGTGCTGCATATGTAGAAGGGAAGTCAAGTGAA
ATGATTGTTACTACTTTAGAATCAGCCCCAAAGGACCCACCTAACACATGACATTTTCAAGAGATACCAGAT
GAAGTTACAAAATTTCAATTAACGTCCTTCTCTCTTCAACCTAATGGAAATATCCAAGTATATCAAGCT
CTGGTTTACCGAGAAGATGATCCTACTGCTGTCAGATTCAACCTCAGTATTATACAGAAAACCAACACA
TTCGTCAATGGCAATGCTAGAAGGACTAAAAGGTGGACATACATACAATATCAGTGTTTACGCACTCAATAGT
GCTGGTGCAGGTCCAAAGGTTCCGATGAGAATAACCATGGATATCAAAGCTCCAGCAGACCAAAAACCAAA
CCAACCCCTATTATGATGCCACAGGAAAATGCTTGTGACTTCAACAACAATTACAAATCAGAAATGCCAATA
TGTTACTACAGTGATGATCATGGACCAATAAAAATGTACAAGTGCTTGTGACAGAAACAGGAGCTCAGCAT
GATGGAATGTAACAAAGTGGTATGATGATATTTTAAATAAGCAAGGCCATATTTTACAAATGAAGGCTTT
CCTAACCTCCTCATGTACAGAAGGAAAGACAAAGTTTAGTGGCAATGAAGAAATCTACATCATAGGTGCTGAT
AATGCATGCATGATTCCTGGCAATGAAGACAAAATTTGCAATGGACCACTGAAACCAAAAAAGCAATACTTA
TTTAAATTTAGAGCTACAAATATTATGGGACAATTTACTGACTCTGATTATTTCTGACCCTGTTAAGACTTTA
GGCGAAGGACTTTTCAAGAAACCTAGAGATCATTTCTTCCGTCACTTTGTGTATCCTTTCAATAATTCTC
CTTGGAAACAGCTATTTTGCATTTGCAAGAATTCGACAGAAAGCAGAAAGGTTGGACATACCTCTCCTCAG
GATGCAGAAATTTATGACACTAAATGAAGCTGGATCAGCTCATCAGTGGCAGACCTGGAAGTGAAGGAC
GAGAGATTAAACGCGGTTACTTAGTTATAGAAAATCCATCAAGCCAATAAGCAAGAAATCTTCTGCAACAT
GTTGAAGAGCTTTGCACAAACAACCACTAAAGTTTCAAGAAGAATTTTCGGAATTACCAAAATTTCTTCAG
GATCTTTCTTCAACTGATGCTGATCTGCCTTGGAAATAGAGCAAAAAACCGCTTCCCAAAACATAAAACCATAT
AATAATAACAGAGTAAAGCTGATAGCTGACGCTAGTGTCCAGGTTCCGATTATATTAATGCCAGCTATATT
TCTGGTATTTTATGTCCAAATGAATTTATTGCTACTCAAGGTCCTACAGGAACAGTTGGAGATTTTTGG
AGAATGGTGTGGAAACCAAGAGCAAAAACATTAGTAATGCTAACACAGTGTTTTGAAAAAGGACGGATCAGA
TGCCATCAGTATTGGCCAGAGGACAACAAGCCAGTTACTGTCTTTGGAGATATAGTGATTACAAAGCTAATG
GAGGATGTTCAAATAGATTGGACTATCAGGGATCTGAAAATGAAAGGCATGGGGATTGCATGACTGCTTCA
CAGTGTAACCTTTACTGCCTGGCCAGAGCATGGGGTTCTGAGAACAGCGCCCTCTAATTCACCTTTGTGAAG
TTGGTTTCGAGCAAGCAGGGCACATGACACCACACCTATGATTGTTCACTGATGTGAGTGGAGTTGGAAGAACT
GGAGTTTTTATTGCTCTGGACCATTTAACACAACATATAAATGACCATGATTTTGTGGATATATATGGACTA
GTAGCTGAACCTGAGAAGTGAAGAATGTGCATGGTGCAGAACTGGCACAGTATATCTTTTTACACCAGTGC
ATTCTGGATCTCTTATCAAATAAGGGAAGTAATCAGCCCATCTGTTTTGTTAACTATTACAGCACTTCAGAAG
ATGGACTCTTTGGACGCCATGGAAGGTGATGTTGAGCTGAAATGGGAAGAAACCACTATGTAA

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In a search of public sequence databases, the NOV2c nucleic acid sequence, located on chromosome 12 has 5903 of 6906 bases (85%) identical to a gb:GENBANK-

ID:AF063249|acc:AF063249.1 mRNA from *Rattus norvegicus* (*Rattus norvegicus* glomerular

5 mesangial cell receptor protein-tyrosine phosphatase precursor (PTPRQ) mRNA, complete

cds) (E =0.0). Public nucleotide databases include all GenBank databases and the GeneSeq patent database.

The disclosed NOV2c polypeptide (SEQ ID NO:10) encoded by SEQ ID NO:9 has 2300 amino acid residues and is presented in Table 2F using the one-letter amino acid code.

- 5 Signal P, Psort and/or Hydropathy results predict that NOV2c has a signal peptide and is likely to be localized in the plasma membrane with a certainty of 0.4600. In other embodiments, NOV2c may also be localized to the microbody (peroxisome) with a certainty of 0.1260, the endoplasmic reticulum (membrane) with a certainty of 0.1000 or in the endoplasmic reticulum (lumen) with a certainty of 0.1000. The most likely cleavage site for a NOV2c peptide is
10 between amino acids 17 and 18, at: SET-QV.

Table 2F. Encoded NOV2c protein sequence (SEQ ID NO:10).	
MDFLIIIFLLFIGTSETQVDVSNVVPGRYDITISSISTYTSPTVTRIVTTNVTPEGPPVFLAGERVGSAGI	
LLSWNTPPNPNGRIISYIVKYKEVCPWMQTVYTQVRSKPDSLEVLLTNLNPGTTYEIKVAAENSAGIGVFS	
PFLFQTAESPAPGKVVNLTVEAYNASAVKLIWYLRQPNKGITSFKISVKHARSIGIVKDVSIREDILT	
LPECNVENSESFLWSTASPSPTLGRVTPPSRTTHSSSTLTQNEISSVWKEPISFVVTHLRPYTTYLFEVS	
AAEAGYIDSTIVRTPESVPEGPPQNCVTGNITGKSFSILWDPPTIVTGKFSYRVELYGPSGRILDNSTKDL	
FAFTNLTPFTMYDVYIAAETSAGTGPKSNISVFTPPDVPDVGAVFDLQAEVESTQVRITWKKPRQPN	
GIINQYRVKVLVPETGIIILENTLLTGNEINDPMAPEIVNIVEPMVGLYEGSAEMSSDLHSLATFIYNSHP	
DKNFARNRAEDQTSPPVTTNRQYITDIAAEQLSYVIRRLVPFTEHMISVSFAFTIMGEGPPTVLSVRTR	
QQVPSSIKIINYKNISSSILLYWDPPEYPNGKITHYTIYAMELDTNRAFQITIDNSFLITGIGLKKYTKY	
KMRVAASTHVGESSLSEENDIFVRTSEDEPESSPDVEVIDVTADEIRLKWSPPEKPNGIITAYEVLYKN	
IDTLYMKNTSTTDIILRNLRPHLTLYNISVRSYTRFGHGNQVSSLLSVRTSETVPDSAPENITYKNIS	
SGEIELSFLPPSSPNGIIQKYTIYLRKRSNGNEERTINTSLTQNLKKYTYIIIEVSASTLKGEVRSAPIS	
SILTEEDAPDSPPDQFSVKQLSGVTVKLSWQPPLEPNGIILYYTVVWRNRSSLTINVTETSLSDLDYNVE	
YSAYVTASTRFGDGKTRSNIIISFQTEGSDPPKDVYANLSSSSIIILFWTPPSKPNGIIQYYSVYRNT	
SGTFMQNFTLHEVTNDFDNMTVSTIIDKLTIFSYFTFWLTAHSVGNNGKSSDIEVYTDQDVPEGFVGNLT	
YESISSTAINSVWVPPAPNGLVFYVYVSLILQQTTPRHVRPPLVYERSIYFDNLEKYTDYILKITPST	
KEGFSDTYTAQLYIKTEEDVPE TSPIINTFKNLSSTSVLLSWDPPVKPNGAIIISYDLTLQGP	
NYSFITSDNYIILEELSPFTLYSFFAAARTRKGLGPSSILFFYTDSEVPLAPPQNLTLINCTSD	
FVWLKWSPLPGGIVKVYSFKIHEHETDTIYYKNISGFKTEAKLVGLEPVSTYSIRVS	
SAFTKVGNGNQFSNVVKFTTQESVPDVVQNMCMATSWQSVLVKWDPPKKANGIITQY	
MVTVERNSTKVSPQDHMYTFIKLLANTS YVFKVRASTSAGEGDESTCHVSTLPETVPSVPTN	
IAFSDVQSTSATLTWIRPDITLGYFQNYKITTLQRAQKCKEWESEECVEYQKIQYLYEAHLTEET	
VYGLKKFRWYRFQVAASTNAGYGNASNWISTKTLPGPPDGPPENVHVATSPFSSISISWSEPA	
VITGPTCYLIDVKSVNDNEFNISFIKSNEENKTIEIKDLEIFTRYSVVITAF	
TGNISAAAYVEGKSSAEMIVTTLESAPKDPPNMTFQKIPDEVTKFQLTSLPPSQPN	
GNIIQVYQALVYREDDPTAVQIHNLISIIQKTNTFVIAMLEGLKGGHTYINISVYAVNS	
AGAGPKVPMRITMDIKAPARPKTKPTPIYDATGKLLVSTTITIRMPICYSDDHGPIKNVQV	
LVLTETGAQHDGNVTKWYDAYFNKARPYFTNEGFPPCTEGTKFSGNEEIIYIGADNAC	
MPGNEDKICNGPLPKKQYLFKFRATNIMGQFTSDSDYSDPVKTLGEGLSERTLEIILSV	
TLCILSIIILGTAFAFARIRQKQKEGGTYSQDAEIIDTKLKLQDLITVADLELKDER	
LTRLLSYRKSIIKPISSKSFQHVVELCTNNLKFQEEFSELPKFLQLDLSSTDADLP	
WNRAKNRFPNIKPYNNRVKLIADASVPGSDYINASYISGYLCPNEFIATQG	
PLPGTVGDFWRMVWETRAKTLVMLTQCFEKGRIHQYWPEDNKPVTVFGDIVITKLMED	
VQIDWTIRDLKIERHGDGMTVRQCNTFAWPEHGVPENSAPLIHFVKLVRASRAHDT	
TPMIVHCSAGVGRGTGVFIALDHLTHQHINDHDFVDIYGLVAELR	
SERMCMVQNLAQYIFLHQCILDLLSNKGSNQPICFVNYSALQKMDSLDAMEGD	
VELEWEETTM	

- A search of sequence databases reveals that the NOV2c amino acid sequence has 1988
of 2301 amino acid residues (86%) identical to, and 2151 of 2301 amino acid residues (93%)
15 similar to, the 2302 amino acid residue ptnr:SPTREMBL-ACC:O88488 protein from *Rattus*
norvegicus (Rat) (Glomerular Mesangial Cell Receptor Protein-Tyrosine Phosphatase

Precursor (EC 3.1.3.48)) (E = 0.0). Public amino acid databases include the GenBank databases, SwissProt, PDB and PIR.

NOV2c is expressed in at least Synovium/Synovial membrane, Kidney. Expression information was derived from the tissue sources of the sequences that were included in the derivation of the sequence of CuraGen Acc. No. CG50718-05. The sequence is predicted to be expressed in the *Rattus norvegicus* :glomerular mesangial. because of the expression pattern of (GENBANK-ID: gb:GENBANK-ID:AF063249|acc:AF063249.1) a closely related *Rattus norvegicus* glomerular mesangial cell receptor protein-tyrosine phosphatase precursor (PTPRQ) mRNA, complete cds homolog.

Homologies among each of the above NOV2 proteins will be shared by the other NOV2 proteins insofar as they are homologous to each other as shown below in Table 2G. Any reference to NOV2 is assumed to refer to all three of the NOV2 proteins in general, unless otherwise noted.

Table 2G Alignment of NOV2a, b, and c

	10	20	30	40	50	60	
NOV2a	MDFLIIIFLLLF	FIGTSETQVDV	SNVVP	TRYDIT	ISSISTTYT	SPVTRI	58
NOV2b	MDFLIIIFLLLF	FIGTSETQVDV	SNVVP	TRYDIT	ISSISTTYT	SPVTRI	1
NOV2c	MDFLIIIFLLLF	FIGTSETQVDV	SNVVP	TRYDIT	ISSISTTYT	SPVTRI	60
	70	80	90	100	110	120	
NOV2a	FLAGERVGSAG	ILLSWNTPP	NPNGRIIS	YIVKYKEV	CPWMQT	VYTQVRS	118
NOV2b	FLAGERVGSAG	ILLSWNTPP	NPNGRIIS	YIVKYKEV	CPWMQT	VYTQVRS	1
NOV2c	FLAGERVGSAG	ILLSWNTPP	NPNGRIIS	YIVKYKEV	CPWMQT	VYTQVRS	120
	130	140	150	160	170	180	
NOV2a	LNP	GTTYEIKVAA	ENSAGIGV	FSDFLFQ	TAEAPGK	VVDFTGE	175
NOV2b	LNP	GTTYEIKVAA	ENSAGIGV	FSDFLFQ	TAEAPGK	VVDFTGE	1
NOV2c	LNP	GTTYEIKVAA	ENSAGIGV	FSDFLFQ	TAEAPGK	VVDFTGE	180
	190	200	210	220	230	240	
NOV2a	ATKKK	KITSEFKIS	VKHNRSG	IIVKES	SIRVECI	LSASLP	235
NOV2b	ATKKK	KITSEFKIS	VKHNRSG	IIVKES	SIRVECI	LSASLP	1
NOV2c	QPNGK	KITSEFKIS	VKHNRSG	IIVKES	SIRVEDI	LTGKLP	240
	250	260	270	280	290	300	
NOV2a	RVTPPSR	THSSSTLT	QNEISSV	KEPISF	VVTHLR	PTYTYL	294
NOV2b	RVTPPSR	THSSSTLT	QNEISSV	KEPISF	VVTHLR	PTYTYL	1
NOV2c	RVTPPSR	THSSSTLT	QNEISSV	KEPISF	VVTHLR	PTYTYL	300
	310	320	330	340	350	360	
NOV2a	RTPE	SVPEGPPQ	NCVTGNI	TGKSFS	ILWDPPT	IVTGKFS	354
NOV2b	RTPE	SVPEGPPQ	NCVTGNI	TGKSFS	ILWDPPT	IVTGKFS	1
NOV2c	RTPE	SVPEGPPQ	NCVTGNI	TGKSFS	ILWDPPT	IVTGKFS	359
	370	380	390	400	410	420	
NOV2a	KFAFT	NLTPFT	MYDVYIA	AETSAGT	GPKSNIS	VFTPPD	414

NOV2b	-----	1
NOV2c	KFAFTNLTPTMYDVYIAAETSAGTGPKSNISVFTPPDVPGA VFDLQLAEVESTQVRITW	419
	430 440 450 460 470 480	
NOV2a	KKPRQPNGIINQYRVKVLVPETGIILENTLLTGNNNEINDPMAPEIVNIVOPMVGLYEGSA	474
NOV2b	-----	1
NOV2c	KKPRQPNGIINQYRVKVLVPETGIILENTLLTGNNNEINDPMAPEIVNIVOPMVGLYEGSA	479
	490 500 510 520 530 540	
NOV2a	EMSSDLHSLATFIYN SHPKNFARNRAEDQTS PVVTRNQYITDIAAEQLTYVIRRLRR	534
NOV2b	-----	1
NOV2c	EMSSDLHSLATFIYN SHPKNFARNRAEDQTS PVVTRNQYITDIAAEQLSYVIRRLVP	539
	550 560 570 580 590 600	
NOV2a	FWAETMGFSRYTIMSSASRDNIISPG-----PLSAQNFRVTHTTIEVFLHWDPEP--PVF	588
NOV2b	-----	1
NOV2c	FTEHMTSVSAFTIMGEGPPTVLSVRTRQOVSSIKIINYKNISSSLLLYWDPEEPYPNGK	599
	610 620 630 640 650 660	
NOV2a	FHLYLITILDVENQSKSIILRTLNLSLVLIIGLKKYTKYKMRVAASTHVGESSLSEENDI	648
NOV2b	-----	1
NOV2c	ITHYTIYAMELDTNRAFOITITIDNSFLITIGLKKYTKYKMRVAASTHVGESSLSEENDI	659
	670 680 690 700 710 720	
NOV2a	FVRTSEDEPESSPQDVEVIDVTADEIRLKWSPPEKPNGIIAYEVLVKNIDTLYMKNTST	708
NOV2b	-----	1
NOV2c	FVRTSEDEPESSPQDVEVIDVTADEIRLKWSPPEKPNGIIAYEVLVKNIDTLYMKNTST	719
	730 740 750 760 770 780	
NOV2a	TDIILRNLRPHPTLYNISVRSYTRFGHGNQVSSLLSVRTSESVPDSAPENITYKNISSGEI	768
NOV2b	-----	1
NOV2c	TDIILRNLRPHPTLYNISVRSYTRFGHGNQVSSLLSVRTSESVV PDSAPENITYKNISSGEI	779
	790 800 810 820 830 840	
NOV2a	ELSFLPPSSPNGIIQKYTIYLRKSNNGNEERTINTTSLTQNIKGLKKYTOYIIIEVSASTLK	828
NOV2b	-----	1
NOV2c	ELSFLPPSSPNGIIQKYTIYLRKSNNGNEERTINTTSLTQNI--LKKYTOYIIIEVSASTLK	837
	850 860 870 880 890 900	
NOV2a	GEGVRSAPISILTEEDAPDSPQDFSVKQLSGVTVKLSWQPPLEPNGIILYYTVYVWR--	886
NOV2b	-----	1
NOV2c	GEGVRSAPISILTEEDAPDSPQDFSVKQLSGVTVKLSWQPPLEPNGIILYYTVYVWRNR	897
	910 920 930 940 950 960	
NOV2a	SSLKTINVTETSLELSDLDYNVEYSAYVTASTRFGDGKTRSNIISFQTPEGPSDPPKDVY	946
NOV2b	-----	1
NOV2c	SSLKTINVTETSLELSDLDYNVEYSAYVTASTRFGDGKTRSNIISFQTPEGPSDPPKDVY	957
	970 980 990 1000 1010 1020	
NOV2a	YANLSSSSIIILFWTPPSKPNGIIQYYSVYYRNTSGTFMQNFTLHEVTNDFDNMTVSTIID	1006
NOV2b	-----	1
NOV2c	YANLSSSSIIILFWTPPSKPNGIIQYYSVYYRNTSGTFMQNFTLHEVTNDFDNMTVSTIID	1017
	1030 1040 1050 1060 1070 1080	
NOV2a	KLTI FSY YTFWLTASTSVGNKSSDIIIEVYTDQDVPEGFVGNLTYESISSTAINVSWVP	1066
NOV2b	-----	26
NOV2c	KLTI FSY YTFWLTASTSVGNKSSDIIIEVYTDQDVPEGFVGNLTYESISSTAINVSWVP	1077
	1090 1100 1110 1120 1130 1140	

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		1810	1820	1830	1840	1850	1860	
5	NOV2a	1846
	NOV2b	806
	NOV2c	1857
		1870	1880	1890	1900	1910	1920	
10	NOV2a	1906
	NOV2b	855
	NOV2c	1917
		1930	1940	1950	1960	1970	1980	
15	NOV2a	1962
	NOV2b	855
	NOV2c	1977
		1990	2000	2010	2020	2030	2040	
20	NOV2a	2017
	NOV2b	855
	NOV2c	2037
25		2050	2060	2070	2080	2090	2100	
	NOV2a	2077
	NOV2b	855
30	NOV2c	2097
		2110	2120	2130	2140	2150	2160	
35	NOV2a	2137
	NOV2b	855
	NOV2c	2157
		2170	2180	2190	2200	2210	2220	
40	NOV2a	2197
	NOV2b	855
	NOV2c	2217
		2230	2240	2250	2260	2270	2280	
45	NOV2a	2257
	NOV2b	855
	NOV2c	2277
50		2290	2300					
	NOV2a					2281 (SEQ ID NO:6)
	NOV2b					855 (SEQ ID NO:8)
55	NOV2c					2300 (SEQ ID NO:10)

The disclosed NOV2a polypeptide has homology to the amino acid sequences shown in the BLASTP data listed in Table 2H.

Table 2H. BLAST results for NOV2a

Gene Index/ Identifier	Protein/ Organism	Length (aa)	Identity (%)	Positives (%)	Expect
gi 12621078 ref NP_075214.1 (NM_022925)	protein tyrosine phosphatase, receptor type, Q [Rattus norvegicus]	2302	1893/2306 (82%)	2077/2306 (89%)	0.0
gi 125977 sp P16621 LAR_DROME	PROTEIN-TYROSINE PHOSPHATASE DLAR PRECURSOR (PROTEIN-TYROSINE-PHOSPHATE PHOSPHOHYDROLASE)	2029	410/1587 (25%)	680/1587 (42%)	1e-94
gi 10728878 gb AAF53837.2 (AE003663)	Lar gene product [Drosophila melanogaster]	2037	410/1587 (25%)	680/1587 (42%)	2e-94
gi 7290546 gb AAF45998.1 (AE003432)	Ptp4E gene product [Drosophila melanogaster]	1767	417/1645 (25%)	694/1645 (41%)	8e-94
gi 1362625 pir A49502	protein-tyrosine-phosphatase (EC 3.1.3.48), receptor type 4E, splice form A precursor - fruit fly (Drosophila melanogaster)	1767	416/1645 (25%)	693/1645 (41%)	1e-92

The homology between these and other sequences is shown graphically in the ClustalW analysis shown in Table 2I. In the ClustalW alignment of the NOV2 proteins, as well as all other ClustalW analyses herein, the black outlined amino acid residues indicate regions of conserved sequence (*i.e.*, regions that may be required to preserve structural or functional properties), whereas non-highlighted amino acid residues are less conserved and can potentially be altered to a much broader extent without altering protein structure or function.

Table 2I. ClustalW Analysis of NOV2

- 1) Novel NOV2a (SEQ ID NO:6)
- 2) gi|12621078|ref|NP_075214.1| (NM_022925) protein tyrosine phosphatase, receptor type, Q [Rattus norvegicus] (SEQ ID NO:37)
- 3) gi|125977|sp|P16621|LAR_DROME PROTEIN-TYROSINE PHOSPHATASE DLAR PRECURSOR (PROTEIN-TYROSINE-PHOSPHATE PHOSPHOHYDROLASE) (SEQ ID NO:38)
- 4) gi|10728878|gb|AAF53837.2| (AE003663) Lar gene product [Drosophila melanogaster] (SEQ ID NO:39)
- 5) gi|7290546|gb|AAF45998.1| (AE003432) Ptp4E gene product [Drosophila melanogaster] (SEQ ID NO:40)
- 6) gi|1362625|pir|A49502 protein-tyrosine-phosphatase (EC 3.1.3.48), receptor type 4E, splice form A precursor - fruit fly (Drosophila melanogaster) (SEQ ID NO:41)

.....10.....20.....30.....40.....50
|.....|.....|.....|.....|.....|.....|.....|.....|.....|

5	NOV2A	-MDFLIIIFLLLFIGTSETQVDVSNVVPCTRYDITISSIS--TTYTSPVTR
	gi 12621078	MMDFHFSFLFLIGTSESQVDVSSSFDGTGYDITLSSVSA-TTYSSPVSF
	gi 125977	-----MGLQMTAARPTAALSLLVLSLLTWHPTIVDAAHPPEIIRK
	gi 10728878	-----MGLQMTAARPTAALSLLVLSLLTWHPTIVDAAHPPEIIRK
	gi 7290546	-MDCATRKQQQLRAHHQCCQIQIQTHGRKRQOQKQRHNNHHHYVQNSQQQ
10	gi 1362625	-MDCATRKQQQLRAHHQCCQIQIQTHGRKRQOQKQRHNNHHHYVQNSQQQ
		60 70 80 90 100
	NOV2A	IGAS--NEPGPPVFLAGERVGSAGILLSWNTPPNPNCRIISVIMKYKEVC
	gi 12621078	TLATNVTKPGPPVFLAGERVGSAGILLSWNTPPNPNCRIISVIMKYKEVC
	gi 125977	PQNGVRVCCVASFYCAARGDPPPSIVWRKNGKKVSG-----
15	gi 10728878	PQNGVRVCCVASFYCAARGDPPPSIVWRKNGKKVSG-----
	gi 7290546	QKHFWLVVGCILITFLAQHANAADLVT--NVFNASSNANAFYRTDYSPPF
	gi 1362625	QKHFWLVVGCILITFLARHANAADLVT--NVFNASSNANAFYRTDYSPPF
		110 120 130 140 150
20	NOV2A	PWMOTIVYTVRSKPDLSLEVLITNINPGTITYEIKVAAENSAGIGVFSDPFL
	gi 12621078	PWMOTAYTRARAKPDSLEVLITNINPGTITYEIKVAAENNAGIGVFSDPFL
	gi 125977	-T-OSRYTVLEQPGCISILRIEPIVRACRDDAPYECVAENGVGDAVSADAT
	gi 10728878	-T-OSRYTVLEQPGCISILRIEPIVRACRDDAPYECVAENGVGDAVSADAT
	gi 7290546	GPEPNTITPASDTC-KDIKFSRALPGTEYNFWIYYTNSTHREOLTWTVN
25	gi 1362625	GPEPNTITPASDTC-KDIKFSRALPGTEYNFWIYYTNSTHREOLTWTVN
		160 170 180 190 200
30	NOV2A	FQTAESAPGKVVDFTGEAVPFSSK-LMYYTS-ATKKKITSEKISVKHNRS
	gi 12621078	FQTAESAPGKVVDLIVEALNYSAVNLITWYLPQNGKITSEKISVKHARS
	gi 125977	LTLYE-----GDKTPAGFPVITGPGTRVIEVGHVIMTCKAIG
	gi 10728878	LTLYEGWQ---KTAISGDKTPAGFPVITGPGTRVIEVGHVIMTCKAIG
	gi 7290546	ITTAPDPP---ANLSVQLRSSKSAFUTWRPP--GSGRYSGERIRVLGLTD
35	gi 1362625	ITTAPDPP---ANLSVQLRSSKSAFUTWRPP--GSGRYSGERIRVLGLTD
		210 220 230 240 250
40	NOV2A	GIVVKEVSIRVECIISASLELHCNENSESFLWSTASPSPTLGRVTPPSRT
	gi 12621078	GIVVKDVSIRVEDILSGKLP-ECNENSESFLWSTTSPSPTLGRVTPVTRT
	gi 125977	NPTPNIYWKNOTKVDMSNPRYSLKDCFLOTENSREEDQGYECVAENSM
	gi 10728878	NPTPNIYWKNOTKVDMSNPRYSLKDCFLOTENSREEDQGYECVAENSM
	gi 7290546	LEFERSYSLEGNETLQLSAK--ELTPGGSYQVQAYSVYQGESVAYTSRN
45	gi 1362625	LEFERSYSLEGNETLQLSAK--ELTPGGSYQVQAYSVYQGESVAYTSRN
		260 270 280 290 300
50	NOV2A	THSSSTLTQNEISSV-KEPISFVVTHLRPYTTYLFVESAITEAGYIDST
	gi 12621078	TQSSSTAARSKISSVWKEPISFVVTHLRPYTTYLFVSAVITEAGYIDST
	gi 125977	GTEHSKATNLVYKVRVPPTFSRPPETISEVMIGSNLNLSCIAVCSMPMH
	gi 10728878	GTEHSKATNLVYKVRVPPTFSRPPETISEVMIGSNLNLSCIAVCSMPMH
	gi 7290546	FTTKPNTPGKFIWFRNETLLVLWQPPFPAGYTHYRVSITPDDATQSV
55	gi 1362625	FTTKPNTPGKFIWFRNETLLVLWQPPFPAGYTHYRVSITPDDATQSV
		310 320 330 340 350
60	NOV2A	IVRTPESVPEGPPONCVTNTITGKSFSILWDPPTIVTGKFSYRVELYGPS
	gi 12621078	IVRTPESVPEGPPONCIMNVTKAESTISWDPPPTIVTGKFSYRVELYGP
	gi 125977	VKWMKGSDDLTPENEMPIGRNVLOLINIQESAN-----
	gi 10728878	VKWMKGSDDLTPENEMPIGRNVLOLINIQESAN-----
	gi 7290546	IYVEREGEPPGPAQAAFKGLVPGRENNISVQT-----
65	gi 1362625	IYVEREGEPPGPAQAAFKGLVPGRENNISVQT-----
		360 370 380 390 400
70	NOV2A	AGRILDNSTKDLKFAFTNLTPTMYDVYVAAETSAAGTGPKSNISVFTPPD
	gi 12621078	SGRILDNSTKDLRFAFTHTLTPTMYDVYVAAETSAAGVGPKSNISVFTPPD
	gi 125977	-----YTICIAASTLCQIDSVSVKVQS
	gi 10728878	-----YTICIAASTLCQIDSVSVKVQS
	gi 7290546	-----VSEDETS-SVPTTARYETVPER
70	gi 1362625	-----VSEDETS-SVPTTARYETVPER

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      410      420      430      440      450
NOV2A  VPCAVFDLQLAEVESQVRLTWKKPRQPNGIINQYRVKVLVPETGIILN
gi|12621078| VPCAVFDLQIAEVEATEIRLTIWRKPRQNGIISQYRVKVSULETGVLIN
5 gi|125977| LPTAPTQVOISEVTATSVRLBWSYKG-----PEDLOYVVICYKPKNAN
gi|10728878| LPTAPTQVOISEVTATSVRLBWSYKG-----PEDLOYVVICYKPKNAN
gi|7290546| VLNVTFDEAYITSSS--FRVRWEPPR---TYSEFDAYQVMLSTSRRIFN
gi|1362625| VLNVTFDEAYITSSS--FRVRWEPPR---TYSEFDAYQVMLSTSRRIFN

      460      470      480      490      500
NOV2A  TLLTGNNR-INDPMAPEIVNIVQPMVGLYEGSAEMSSDLHSLATFIYNH
gi|12621078| TLLTGQDEISISNPMSP EIMNLVDPMICHYEGSGEMSSDLHSPASFIYNH
gi|125977| QAFSEISG---IITMYVVRALSPYTEYEFYVIAVNNIGRG-----
15 gi|10728878| QAFSEISG---IITMYVVRALSPYTEYEFYVIAVNNIGRG-----
gi|7290546| VPRANGD---SVYFDYPDILEPGRTYEVVVKTIADNVN-----
gi|1362625| VPRANGD---SVYFDYSDILEPGRTYEVVVKTIADNVN-----

      510      520      530      540      550
NOV2A  PDKNFPAARNRAEDQTSPPVITRNQYITDIAAEQLTYVLIRLRRFWAETMG
gi|12621078| PHNDFPASTRAEQSSPPVITRNQYMTDITAEQLSYVVRRLVPFTEHTIS
gi|125977| -----PPSAPATCTIGETKMESAP-----
20 gi|10728878| -----PPSAPATCTIGETEMESAP-----
25 gi|7290546| ---SWPASGEVTLRPRPVRLG-----
gi|1362625| ---SWPASGEVTLRPRPVRLG-----

      560      570      580      590      600
NOV2A  FSRYTIMSSASRDNLTSFG---PLSAQNFVRVTHVTILEVFIHWPPDPV
gi|12621078| VSAFTIMGEGPPTVLTVRTREQVPSSIQIINYNKISSSILLYWDPPEYP
gi|125977| -----RNVQVRTLSSTMTVITWEPPETP
30 gi|10728878| -----RNVQVRTLSSTMTVITWEPPETP
gi|7290546| -----GFLDDR---SNALHISWEPAETG
35 gi|1362625| -----GFLDDR---SNALHISWEPAETG

      610      620      630      640      650
NOV2A  FFHHYLITILDVENQSKS---IILRTLNSLSLVIGLKKYTKYKMRVAA
40 gi|12621078| NGKITHYITITATELDINR---AFQMTTVDNSFLITGLKKYTRYKMRVAA
gi|125977| NGQVTGYKVYYTINSNQPEASWNSQMDNSBELTTVSDVTEPHATYTVRVOA
gi|10728878| NGQVTGYKVYYTINSNQPEASWNSQMDNSBELTTVSELTTPHATYTVRVOA
45 gi|7290546| RQDSYRISYHEQTNASEV---PAPFPVAABESQITINLTETLDSL LAGR
gi|1362625| RQDSYRISYHEQTNASEV---PAPFPVAABESQITINLTETLDSL LAGR

      660      670      680      690      700
NOV2A  STHVGESSLSSEENDIFVRTSEDEPESSQDVEIDVTADEIRLKWSPPEK
50 gi|12621078| STHVGESSLSSEENDIFVRTPEDEPESSQDQVQTGVSPSELRLKWSPPEK
gi|125977| YTSMCAGPMSTP-----
gi|10728878| YTSMCAGPMSTP-----
60 gi|7290546| RYLTAVQALSKG-----
gi|1362625| RYLTAVQALSKG-----

      710      720      730      740      750
NOV2A  PNGIIIAEVLYKNIDTLYMKNTSTTDIILRNLRPHLYNISVRSYTRFG
65 gi|12621078| PNGIIIAEVLYQNADTLFVKNTSTTDIIISDLKPYTLYNISIRSYTRLG
gi|125977| -----VQVKAQQGVF-----
60 gi|10728878| -----VQVKAQQGVF-----
gi|7290546| -----VASNASDIT-----R-YTRP-
gi|1362625| -----VASNASDIT-----R-YTRP-

      760      770      780      790      800
NOV2A  HGNQVSSLLSVRTSESVPDSAPENITYKNISSCEIEISLPPSPNGIITQ
70 gi|12621078| HGNQSSSLLSVRTSETVPDSAPENITYKNISSCEIEISLPPSPNGIITQ
gi|125977| -----SQPSNFRATDICTATVLTQWTKPTHSSSENTV
gi|10728878| -----SQPSNFRATDICTATVLTQWTKPTHSSSENTV
gi|7290546| -----AAPLIQELRSIDQG---LMLSWRSDVNSRQD

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gi | 1362625 |AAPLIQELRSLDQC.....LMLSWRSDVNSRQD

810 820 830 840 850

5 NOV2A KYTITLKRNSNG-NEERTINTTSLTQNIKGLKKYTCVLTIEVSASTLKGEGV
gi | 12621078 | KYTITLKRNSNS-HEARTINTTSLTQTIGGLKKYTHVTVIEVSASTLKGEGV
gi | 125977 | HYELVWNDIYANQAAHKKRISNSEAYTLDGLYPDITLYIWLAAORSORGECA
gi | 10728878 | HYELVWNDIYANQAAHKKRISNSEAYTLDGLYPDITLYIWLAAORSORGECA
gi | 7290546 | RYEVHYQRNGT-REERTMATNETSLTIHYLHPGSGYEVKVVHAISH---GV
gi | 1362625 | RYEVHYQRNGT-REERTMATNETSLTIHYLHPGSGYEVKVVHAISH---GV

860 870 880 890 900

15 NOV2A RSAPISILITEEDAPDSPPQDFSVKQLSGVTVKLSWQPP--LEPNCIILYY
gi | 12621078 | RSAPISILITEEDAPDSPPQDFSVKQLSGVTVMLSWQPP--LEPNCIILYY
gi | 125977 | TTPPIPVRTKQYVPGAPPRNITAIATSSITITLSLWLPVPVERNGRIITYY
gi | 10728878 | TTPPIPVRTKQYVPGAPPRNITAIATSSITITLSLWLPVPVERNGRIITYY
gi | 7290546 | RSEPHSYFQAVFP--KPPONLTQTVHTNLVVLHWCAP--EGSD-FSEYV
gi | 1362625 | RSEPHSYFQAVFP--KPPONLTQTVHTNLVVLHWCAP--EGSD-FSEYV

910 920 930 940 950

25 NOV2A TVYVWR---SSLKTIN-VTETSILELSLDLYNVESAYVITASTRFGDGKT
gi | 12621078 | TVYVWDK---SSLKAIN-ATEASIVLSLDLYNVQYACVITASTRFGDGNA
gi | 125977 | KVFVFEVGREDDDEATMTLNMSTIVLDELKRWTEYKIWVLACTSVGDCG-P
gi | 10728878 | KVFVFEVGREDDDEATMTLNMSTIVLDELKRWTEYKIWVLACTSVGDCG-P
gi | 7290546 | VRVRTDA---SPWQRTISGLHENEARTKDMHYGERLYVQVNTVS-FGVESP
gi | 1362625 | VRVRTDA---SPWQRTISGLHENEARTKDMHYGERLYVQVNTVS-FGVESP

960 970 980 990 1000

35 NOV2A RSNIIISFCITPEG-PSDPPKDVYYANLSSSSIIILFWTPPS--KPNGIIQYY
gi | 12621078 | RSNIIINFTPEGEPSDPPNDVHYVNLSSSSIIILFWTPPV--KPNGIIQYY
gi | 125977 | RSHPIILRTQEDVPGD-PODVKATPLNSTSIHVSWMKPPLEKDRNGIIRGY
gi | 10728878 | RSHPIILRTQEDVPGD-PODVKATPLNSTSIHVSWMKPPLEKDRNGIIRGY
gi | 7290546 | HPLELNVMTMPQ----PVSNNVPLVDSRNLTLEMP----REDCHVDFY
gi | 1362625 | HPLELNVMTMPQ----PVSNNVPLVDSRNLTLEMP----REDCHVDFY

1010 1020 1030 1040 1050

40 NOV2A SVYYRNTSGTFMQNFTLHEVTNDFDNMTVSTIIDKLTIFSYYTFWLTAST
gi | 12621078 | SVYYQNTSGTFVQNFTLLQVTKESDNVTVSARIYRLAIFSYYTFWLTAST
gi | 125977 | -----
gi | 10728878 | -----
gi | 7290546 | -----
gi | 1362625 | -----

1060 1070 1080 1090 1100

50 NOV2A SVGNNGNKSSDIIIEVYTDQDVPEGFVGNLTYESISSTAINMSWVPPAPNG
gi | 12621078 | SVGNNGNKSSDIIHVTQDQIPEGPVGNLTFESISSTAIHVSWEPPSQPNG
gi | 125977 | -----HTHAQELRDEC
gi | 10728878 | -----HTHAQELRDEC
gi | 7290546 | -----TKKWPTDEEDR
gi | 1362625 | -----TKKWPTDEEDR

1110 1120 1130 1140 1150

60 NOV2A TVFYFVSLILQQLP-RHVRPPLVTYERSITYFONLEKYTDYILKTIPTSTBK
gi | 12621078 | TVFYFVSLNLQOSPPRHMIPPLVTYENSTDFDLEKYTDYIFKTIPTSTBK
gi | 125977 | KGFLENEPFKFDVVD-----TLEFNVMTGLQPDTKYSIQVAALTRK
gi | 10728878 | KGFLENEPFKFDVVD-----TLEFNVMTGLQPDTKYSIQVAALTRK
gi | 7290546 | VEFKNVITQLEDLSS-----P---SVRIPTEDLSEGGROYRFEVQASSN-
gi | 1362625 | VEFKNVITQLEDLSS-----P---SVRIPTEDLSEGGROYRFEVQASSN-

1160 1170 1180 1190 1200

70 NOV2A GFSPTTYTAQYLIKTEEDIPETSPIDNTFNLSSTSVLLSWDPEVKNPCAT
gi | 12621078 | GFSPTTYTQHLIKTEEDVDPDTPPIDNTFNLSSTSVLLSWDPELKNPCAT
gi | 125977 | CDGDRSAAIVVKTPCGVVPVRPTVSLKIMEREPIVSHLELEWERRPACTYCEL

gi | 10728878 | C G C G R S A A I V V K T P C G V P V R P T V S K I M E R E P I V S T E L E W E R P A Q T Y C E T
gi | 7290546 | C ----- I R S C ----- T
gi | 1362625 | C ----- I R S C ----- T

5

1210 1220 1230 1240 1250

NOV2A I S V D L T L ----- O G P N E N Y S F I T S D N Y I L L E L S P F T L Y S F F A A A R T R K G I
gi | 12621078 | L G Y H L T L ----- O G P H A N H T F V T S G N H I V L E L S P F T L Y S F F A A A R T M K G I
gi | 125977 | R G Y R L R W G V K D Q A L K E E M L S G P Q M T K K R F D N L E R G V E Y E F R V A G S N H I G I
gi | 10728878 | R G Y R L R W G V K D Q A L K E E M L S G P Q M T K K R F D N L E R G V E Y E F R V A G S N H I G I
gi | 7290546 | ----- T H L S T R T M P L I Q S D V F I A N A G H E Q Q
gi | 1362625 | ----- T H L S T R T M P L I Q S D V F I A N A G H E Q Q

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1260 1270 1280 1290 1300

NOV2A G P S S I L F Y T D E S V P L A P P O N L T L I N C T S D F V W L K W S P S P L P G G I V K V Y S
gi | 12621078 | G P S S I L F Y T D E S A P L A P P O N L T L I N Y T S D F V W L I W S P S P L P G G I V K V Y S
gi | 125977 | G Q E T V K I F Q T P E G T P G G P P S N I T I R F Q T P D V L C V I W D P P T R E H R N G I T I R
gi | 10728878 | G Q E T V K I F Q T P E G T P G G P P S N I T I R F Q T P D V L C V I W D P P T R E H R N G I T I R
gi | 7290546 | ----- D E T I T L S Y T P T P A D S T R F D I Y R
gi | 1362625 | ----- D E T I T L S Y T P T P A D S T R F D I Y R

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1310 1320 1330 1340 1350

NOV2A F K D H E H E T D T I Y Y K N I S G F K T E A K L V G L E P V S T Y S I R V S A F T K V G N G N Q F
gi | 12621078 | F K D H E H E T D T V F Y K N I S G L Q T D A K L E G L E P V S T Y S V S V S A F T K V G N G N Q Y
gi | 125977 | Y D V Q F H -----
gi | 10728878 | Y D V Q F H -----
gi | 7290546 | R S M G D -----
gi | 1362625 | R S M G D -----

20

1360 1370 1380 1390 1400

NOV2A S N V V K F T T Q E S V P D V V Q N M Q C M A T S W Q S V L V K W D P P K K A N G I I T Q Y M V T V
gi | 12621078 | S N V V E F T T Q E S V P E A V R N I E C V A R D W Q S V S V R W D P P R K T N G I I I H Y M I T V
gi | 125977 | ----- K K ----- I D
gi | 10728878 | ----- K K ----- I D
gi | 7290546 | ----- P ----- T I
gi | 1362625 | ----- P ----- T I

25

1410 1420 1430 1440 1450

NOV2A E R N S T K V S P O D H M Y T F I K L L A N T S Y V F K V R A S T S A G E C D E S T C H V S T I P E
gi | 12621078 | G G N S T K V S P R D P T Y F I K L L P N T S Y V E F V R A S T S A G E G N E S R C D I S T I P E
gi | 125977 | H G L G S E R M M T L R K A V F I N L E E N T E Y I F R V R A Y T K Q G A C P F S D K L I V E T E R
gi | 10728878 | H G L G S E R M M T L R K A V F I N L E E N T E Y I F R V R A Y T K Q G A C P F S D K L I V E T E R
gi | 7290546 | K D K E K L A N D T E R K L S F S G L T P G K L Y N V T V T V S ----- G G V A S L P V Q R I Y R
gi | 1362625 | K D K E K L A N D T E R K L S F S G L T P G K L Y N V T V T V S ----- G G V A S L P V Q R I Y R

30

1460 1470 1480 1490 1500

NOV2A T V P S V P T N I A F S D V Q S T S A T L T W I R P D T I L G Y F Q N Y K I T T O L R A C K C K E W
gi | 12621078 | T V P S A P T N V A F S N V Q S T S A T L T W T K R D T I F G Y F Q N Y K I T T O L R A C K C R E W
gi | 125977 | D M G R A P S L Q A E A T S E Q T A E T W W E P V T S R G K L L G Y I F Y M T A V E -----
gi | 10728878 | D M G R A P S L Q A E A T S E Q T A E T W W E P V T S R G K L L G Y I F Y M T A V E -----
gi | 7290546 | L H L P L S D L K A I Q V A A R E I T L H W T A P A G E Y T D F E L Q Y L S A D E E A P -----
gi | 1362625 | L H L P L S D L K A I Q V A A R E I T L H W T A P A G E Y T D F E L Q Y L S A D E E A P -----

35

1510 1520 1530 1540 1550

NOV2A E S E E C V E Y Q K I Q Y I Y E A H L T E E T V Y G L K K F R W Y R F Q V A A S T N A G Y N G N A S N
gi | 12621078 | E P E E C I E H Q K D Q Y I Y E A N C T E E T V H G L K K F R W Y R F Q V A A S T N V G Y S N A S E
gi | 125977 | ----- D L D D W Q T K T V G L T E S A D L V N L E K F A Q Y A V A I A A R F K N G I G R L S E
gi | 10728878 | ----- D L D D W Q T K T V G L T E S A D L V N L E K F A Q Y A V A I A A R F K N G I G R L S E
gi | 7290546 | ----- Q L L Q N ----- V T K N ----- T E I T L Q G L R P Y H N Y T F T V V V R S G S ----- I Q G -----
gi | 1362625 | ----- Q L L Q N ----- V T K N ----- T E I T L Q G L R P Y H N Y T F T V V V R S G S ----- I Q G -----

40

1560 1570 1580 1590 1600

NOV2A W I S T R T L P G P P D G P P E N V H V A T S P F S I S T S W S E P A V I T G E T C Y L L D V K S

5	gi 12621078	WISTQTLPGPDPGPPENVHVATSPFGINISWSSEAVITGPTFYLTIDVKS
	gi 125977	KVTVRIK---PEDVPLNLRADHVSHTSMTLSWSPPHRLT-PVNYKISFDA
	gi 10728878	KVTVRIK---PEDVPLNLRADHVSHTSMTLSWSPPHRLT-PVNYKISFDA
	gi 7290546	TDFADVSVSTLMRSSAPISASVQTLTAPPCKVDYFQPSD-
	gi 1362625	-----TDFADVSVSTLMRSSAPISASVQTLTAPPCKVDYFQPSD-
10	NOV2A1610.....1620.....1630.....1640.....1650
	gi 12621078	VNDDEFNISFIKSNEENKTIKDLKLEIFTRYSVVITAFVGNVSRAYTDGK
	gi 125977	VDDDDFNISFLKSNEENKTEINNLEVFTRYSVVITAFVGNVSRAYTDGK
	gi 10728878	MK-----
	gi 7290546	MK-----
	gi 1362625	VQ-----
15	NOV2A1660.....1670.....1680.....1690.....1700
	gi 12621078	SSAEMIVTTLESAPKDPNNMTFQKIPDEVTKFQLTFLPPSQPNQNTQVY
	gi 125977	SSAEVIITTTLESVPKDPNNMTFQKIPDEVTKFQLTFLPPSQPNQNTQVY
	gi 10728878	-----VFVDSQGFSTQ-----QIVPKREIILKH
	gi 7290546	-----VFVDSQGFSTQ-----QIVPKREIILKH
	gi 1362625	-----PGEVTFEWS-----LEPAEQHCPTDYF
20	NOV2A1710.....1720.....1730.....1740.....1750
	gi 12621078	QALVYREDPTAVQIHNLSTIQKNTNFVIAMLEGLKGCHTYNISVYVNS
	gi 125977	QALVYREDPTAVQIHNLSTIQKNTNFVIAMLEGLKGCHTYNISVYVNS
	gi 10728878	YVKTHITINELSPFTTYNNVNSAIPS-----DYSYRPPTKITVTIQMAAPQ
	gi 7290546	YVKTHITINELSPFTTYNNVNSAIPS-----DYSYRPPTKITVTIQMAAPQ
	gi 1362625	RITCONADDAADVSSYEFPVNATQG-----KIDGLVPCNHYIFRTOAKSA
25	NOV2A1760.....1770.....1780.....1790.....1800
	gi 12621078	ACACPKVPMRITMDIKAPAREKTKPTIDYDAGKLLVTSITITIRMPICY
	gi 125977	ACACPKVQMRITMDIKAPAREKSKPIETRDATGKLLVTSITITIRMPICY
	gi 10728878	PMVKPDIFYGVNGEELVLVLPQASEEYGPISH-----YYLVVVPEDKSN
	gi 7290546	LCYCAERHITQTMPIILAPPVPEPSVTPEVSR-----TSSTIETSFROGY
	gi 1362625	LCYCAERHITQTMPIILAPPVPEPSVTPEVSR-----TSSTIETSFROGY
30	NOV2A1810.....1820.....1830.....1840.....1850
	gi 12621078	YSDDHCPTRNVQVLTETGAQHDG--NVTKNYDAYFNKAR-PYFTNECEP
	gi 125977	YNDHCPTRNVQVLTETGAQODG--NVTKNYDAYFNKAR-PYFTNECEP
	gi 10728878	LHKIPDQFLIDDLTPGRNKPFRPN---APYIAAKFPORSIPETFHLGSG
	gi 7290546	LHKIPDQFLIDDLTPGRNKPFRPN---APYIAAKFPORSIPETFHLGSG
	gi 1362625	FSNAHGMVRSYTIILADGVGNASGLEMPSONDVCAYTVWLIPYQAIPEYN
35	NOV2A1860.....1870.....1880.....1890.....1900
	gi 12621078	NPPCTECKTKFSGNEEIIYLIGADNACMIPGNEEKICNGPLKPKKOYLFKF
	gi 125977	NPPCIECKTKFSGNEEIIYLIGADNACMIPGNEEKICNGPLKPKKOYLFKF
	gi 10728878	DDYHNFTRKLEREKRYRIFVRAVVDTPQK---LYTSSPFSEFLSLDMRE
	gi 7290546	PFLTSGSRKSSLEAEHFTIGTANCDKHQAG---YCNGPLRAGTTRYRIKI
	gi 1362625	PFLTSGSRKSSLEAEHFTIGTANCDKHQAG---YCNGPLRAGTTRYRIKI
40	NOV2A1910.....1920.....1930.....1940.....1950
	gi 12621078	RATNIMGQFTDSYSDPVTLGEGLSERIVETILSVTLCLLSIILLGTAI
	gi 125977	RATNVMGQFTDSYSDPVTLGEGLSERIVETILSVTLCLLSIILLGTAI
	gi 10728878	APPGERPHRPDPNWPPEPEVSVNRNKCEPEILWVVLPLMVSIFIVSTALI
	gi 7290546	APPGERPHRPDPNWPPEPEVSVNRNKCEPEILWVVLPLMVSIFIVSTALI
	gi 1362625	RAFTDEDKFTDVIYSSPTITE-----R-SDTVIVAAIVSAVLEVAVVLVV
45	NOV2A1960.....1970.....1980.....1990.....2000
	gi 12621078	RAFTDEDKFTDVIYSSPTITE-----R-SDTVIVAAIVSAVLEVAVVLVV

5 NOV2A FAFARIROKQ-----KEGGTYSPQDAEITDTKLKLDLELITVALELEKDER
gi|12621078| FAFVRIROKQ-----KEGGTYSPRDAEITDTKFLDOLLITVALELEKDER
gi|125977| VLCVVKKRRROPCKTPDQAAVTRFLMAADLGAGPTSPDPVDMRRLNFQPTG
gi|10728878| VLCVVKKRRROPCKTPDQAAVTRFLMAADLGAGPTSPDPVDMRRLNFQPTG
gi|7290546| VYCOHRCOLI-----RRASKLAR-----MODELAAAPLEGYITPN-
gi|1362625| VYCOHRCOLI-----RRASKLAR-----MODELAAAPLEGYITPN-

10 2010 2020 2030 2040 2050
NOV2A IT-----RPIISKKSFLQHVLEELCINNNLKFEFEFSELPKFLDQLSS
gi|12621078| ITRLLSYRKSIKPIISKKSFLQHVLEELCINNNLKFEFEFSELPKFLDQLSS
gi|125977| MIS-----HPPIPTISEFANHTIERLKSNDNQKFSQEYESIEFG-QQFTW
gi|10728878| MIS-----HPPIPTISEFANHTIERLKSNDNQKFSQEYESIEFG-QQFTW
gi|7290546| -----RPVHVKDFSEBYRIMSADSDFFPSEEFEEELKHVGRDOAC
gi|1362625| -----RPVHVKDFSEBYRIMSADSDFFPSEEFEEELKHVGRDOAC

15 2060 2070 2080 2090 2100
NOV2A ITDADLPNNRAKNRFPNIKPYNNNRVKLIADASVPGSDYINASYISGYLCP
gi|12621078| ITDADLPNNRAKNRFPNIKPYNNNRVKLIADVSLPGSDYINASYISGYLCP
gi|125977| DNSNLEHNKSKNRNANYTAYDHSRVLPAVEGVVGSYDINANYCDGYRKH
gi|10728878| DNSNLEHNKSKNRNANYTAYDHSRVLPAVEGVVGSYDINANYCDGYRKH
gi|7290546| SFANLPQNRPKNRFTNILPYDHSRFLQPVDDDDGSDYINANYMPCGNSF
gi|1362625| SFANLPQNRPKNRFTNILPYDHSRFLQPVDDDDGSDYINANYMPCGNSF

20 2110 2120 2130 2140 2150
NOV2A NEFIATQGPLPGTVGDFWRMVVETRAKTIIVMLTQCFEKGRIKCHOYWPEP
gi|12621078| NEFIATQGPLPGTVGDFWRMVVETRTKTIIVMLTQCFEKGRIKCHOYWPEP
gi|125977| NAYVATQGPLETTFVDFWRMCWELKTATIVMMTRLEERTRIKCDQYWPTR
gi|10728878| NAYVATQGPLETTFVDFWRMCWELKTATIVMMTRLEERTRIKCDQYWPTR
gi|7290546| REFIVTQGPLHSTREEFFWRMCWESNSRAIVMLTRCFEKGREKCDQYWPVD
gi|1362625| REFIVTQGPLHSTREEFFWRMCWESNSRAIVMLTRCFEKGREKCDQYWPVD

25 2160 2170 2180 2190 2200
NOV2A NKPVTVFGDIVITKLMEVDQIDWTIIRDLKTERH--GDCMTVROCNETTWP
gi|12621078| NKPVTVFGDIVITKLMEVDQIDWTIIRDLKTERH--GDCMTVROCNETTWP
gi|125977| G--TETYGQIFVTITETQELATYSIRTFQLCROGFNDRETKOLOFTWAP
gi|10728878| G--TETYGQIFVTITETQELATYSIRTFQLCROGFNDRETKOLOFTWAP
gi|7290546| R-VAMFYGDIKVQLIIDTHYHWSISEFMVSRN--CESRIMRHFFFTTWP
gi|1362625| R-VAMFYGDIKVQLIIDTHYHWSISEFMVSRN--CESRIMRHFFFTTWP

30 2210 2220 2230 2240 2250
NOV2A DHGVPENSAPLIHVFVKLVRSRAHDITPMIVHCSAGVGRTCGYIIVIDSML
gi|12621078| DHGVPENTTPLIHVFVKLVRSRAHDITPMIVHCSAGVGRTCGYIIVIDSML
gi|125977| DHGVPDHPAPFLQFLRRCRALTTPESGPVIVHCSAGVGRTCGYIIVIDSML
gi|10728878| DHGVPDHPAPFLQFLRRCRALTTPESGPVIVHCSAGVGRTCGYIIVIDSML
gi|7290546| DFGVPEPQSLVRFVRAFRDVIIGTDMRPIIVHCSAGVGRSGCIFIALDRIL
gi|1362625| DFGVPEPQLSLVRFVRAFRDVIIGTDMRPIIVHCSAGVGRSGCIFIALDRIL

35 2260 2270 2280 2290 2300
NOV2A QHINDHDFVDIYGLVAELRSEKCMVQNLAQYIFLHQCILOLLS-----
gi|12621078| QHINNHDVVDIYGLVAELRSEKCMVQNLAQYIFLHQCILOLLS-----
gi|125977| ERMKHEKILDIYGHVTCCLRACRNVMVQTEQYIFIHDAILEAIIICG---
gi|10728878| ERMKHEKILDIYGHVTCCLRACRNVMVQTEQYIFIHDAILEAIIICG---
gi|7290546| QHIHKSQYVDIFGIVFAMRKERVFMVQTEQYQYVCIHQCLLAIVLEGKEHLL
gi|1362625| QHIHKSQYVDIFGIVFAMRKERVFMVQTEQYQYVCIHQCLLAIVLEGKEHLL

40 2310 2320 2330 2340 2350
NOV2A -----NKGSNQPICFVNYSALOKMDSLDAAMEGGDVELEWEETITM-----
gi|12621078| -----NKGGHQPVCEVNYSTLQKMDSLDAMEG-DVELEWEETITM-----
gi|125977| --VTEVPARNLHHTHLOKLLITTEPGETISGMEVEFKKLSNVMKDSKVFVTA
gi|10728878| --VTEVPARNLHHTHLOKLLITTEPGETISGMEVEFKKLSNVMKDSKVFVTA
gi|7290546| ADSLELHANDGVEVTKIYLERQPTKMGILPTRASLAMAELDADLMTNK
gi|1362625| ADSLELHANDGVEVTKIYLERQPTKMGILPTRASLAMAELDADLMTNK

45 2360 2370 2380 2390 2400
NOV2A -----NKGSNQPICFVNYSALOKMDSLDAAMEGGDVELEWEETITM-----
gi|12621078| -----NKGGHQPVCEVNYSTLQKMDSLDAMEG-DVELEWEETITM-----
gi|125977| --VTEVPARNLHHTHLOKLLITTEPGETISGMEVEFKKLSNVMKDSKVFVTA
gi|10728878| --VTEVPARNLHHTHLOKLLITTEPGETISGMEVEFKKLSNVMKDSKVFVTA
gi|7290546| ADSLELHANDGVEVTKIYLERQPTKMGILPTRASLAMAELDADLMTNK
gi|1362625| ADSLELHANDGVEVTKIYLERQPTKMGILPTRASLAMAELDADLMTNK

50 2410 2420 2430 2440 2450
NOV2A -----NKGSNQPICFVNYSALOKMDSLDAAMEGGDVELEWEETITM-----
gi|12621078| -----NKGGHQPVCEVNYSTLQKMDSLDAMEG-DVELEWEETITM-----
gi|125977| --VTEVPARNLHHTHLOKLLITTEPGETISGMEVEFKKLSNVMKDSKVFVTA
gi|10728878| --VTEVPARNLHHTHLOKLLITTEPGETISGMEVEFKKLSNVMKDSKVFVTA
gi|7290546| ADSLELHANDGVEVTKIYLERQPTKMGILPTRASLAMAELDADLMTNK
gi|1362625| ADSLELHANDGVEVTKIYLERQPTKMGILPTRASLAMAELDADLMTNK

55 2460 2470 2480 2490 2500
NOV2A -----NKGSNQPICFVNYSALOKMDSLDAAMEGGDVELEWEETITM-----
gi|12621078| -----NKGGHQPVCEVNYSTLQKMDSLDAMEG-DVELEWEETITM-----
gi|125977| --VTEVPARNLHHTHLOKLLITTEPGETISGMEVEFKKLSNVMKDSKVFVTA
gi|10728878| --VTEVPARNLHHTHLOKLLITTEPGETISGMEVEFKKLSNVMKDSKVFVTA
gi|7290546| ADSLELHANDGVEVTKIYLERQPTKMGILPTRASLAMAELDADLMTNK
gi|1362625| ADSLELHANDGVEVTKIYLERQPTKMGILPTRASLAMAELDADLMTNK

60 2510 2520 2530 2540 2550
NOV2A -----NKGSNQPICFVNYSALOKMDSLDAAMEGGDVELEWEETITM-----
gi|12621078| -----NKGGHQPVCEVNYSTLQKMDSLDAMEG-DVELEWEETITM-----
gi|125977| --VTEVPARNLHHTHLOKLLITTEPGETISGMEVEFKKLSNVMKDSKVFVTA
gi|10728878| --VTEVPARNLHHTHLOKLLITTEPGETISGMEVEFKKLSNVMKDSKVFVTA
gi|7290546| ADSLELHANDGVEVTKIYLERQPTKMGILPTRASLAMAELDADLMTNK
gi|1362625| ADSLELHANDGVEVTKIYLERQPTKMGILPTRASLAMAELDADLMTNK

65 2560 2570 2580 2590 2600
NOV2A -----NKGSNQPICFVNYSALOKMDSLDAAMEGGDVELEWEETITM-----
gi|12621078| -----NKGGHQPVCEVNYSTLQKMDSLDAMEG-DVELEWEETITM-----
gi|125977| --VTEVPARNLHHTHLOKLLITTEPGETISGMEVEFKKLSNVMKDSKVFVTA
gi|10728878| --VTEVPARNLHHTHLOKLLITTEPGETISGMEVEFKKLSNVMKDSKVFVTA
gi|7290546| ADSLELHANDGVEVTKIYLERQPTKMGILPTRASLAMAELDADLMTNK
gi|1362625| ADSLELHANDGVEVTKIYLERQPTKMGILPTRASLAMAELDADLMTNK

70 2610 2620 2630 2640 2650
NOV2A -----NKGSNQPICFVNYSALOKMDSLDAAMEGGDVELEWEETITM-----
gi|12621078| -----NKGGHQPVCEVNYSTLQKMDSLDAMEG-DVELEWEETITM-----
gi|125977| --VTEVPARNLHHTHLOKLLITTEPGETISGMEVEFKKLSNVMKDSKVFVTA
gi|10728878| --VTEVPARNLHHTHLOKLLITTEPGETISGMEVEFKKLSNVMKDSKVFVTA
gi|7290546| ADSLELHANDGVEVTKIYLERQPTKMGILPTRASLAMAELDADLMTNK
gi|1362625| ADSLELHANDGVEVTKIYLERQPTKMGILPTRASLAMAELDADLMTNK

		2360	2370	2380	2390	2400
	NOV2A				
5	gi 12621078	-----				
	gi 125977	NLPCNKHKNNRLVHLLPYESSRVYLTPIHGIEGSDYVNASFIDGYRYSAY				
	gi 10728878	NLPCNKHKNNRLVHLLPYESSRVYLTPIHGIEGSDYVNASFIDGYRYSAY				
	gi 7290546	DEDEDQEEQQQQQQQ-----LATEVKKPKGSN				
10	gi 1362625	DEDEDQEEQQQQQQQ-----LATEVKKPKGSN				
		2410	2420	2430	2440	2450
	NOV2A				
15	gi 12621078	-----				
	gi 125977	IAAGCPVQDAAEDFWRMLWEHNSITIVMLTKLKEMGREKCFQYWPHERSV				
	gi 10728878	IAAGCPVQDAAEDFWRMLWEHNSITIVMLTKLKEMGREKCFQYWPHERSV				
	gi 7290546	DDEEDEEDDDDDDDCOPLNNETTATLSSASCSSS-----THDVHV				
	gi 1362625	DDEEDEEDDDDDDDCOPLNNETTATLSSASCSSS-----THDVHV				
20		2460	2470	2480	2490	2500
	NOV2A				
25	gi 12621078	-----				
	gi 125977	RYQYYVVDPIAEYNMPQYKLREFKVTDAARDGSSRTVRQFQFIDWPEOCVP				
	gi 10728878	RYQYYVVDPIAEYNMPQYKLREFKVTDAARDGSSRTVRQFQFIDWPEOCVP				
	gi 7290546	VLCEATEKPKQERICAGTQSHADTESDNTDSDDDDDEGDGKVAKDCAV				
	gi 1362625	VLCEATEKPKQERICAGTQSHADTESDNTDSDDDDDEGDGKVAKDCAV				
30		2510	2520	2530	2540	2550
	NOV2A				
	gi 12621078	-----				
	gi 125977	KSGEGFIDFIGQVHKTEQFGQDGPITVHCSAGVGRSGVFITLSIVLERM				
	gi 10728878	KSGEGFIDFIGQVHKTEQFGQDGPITVHCSAGVGRSGVFITLSIVLERM				
35	gi 7290546	ADEDCGWY-----				
	gi 1362625	ADEDCGWY-----				
40		2560	2570	2580	2590	
	NOV2A				
	gi 12621078	-----				
	gi 125977	QYEGVLDVFQTVRILRSQRPA MVQTEDQYHFCYRAALEYLGSFDNYTN				
	gi 10728878	QYEGVLDVFQTVRILRSQRPA MVQTEDQYHFCYRAALEYLGSFDNYTN				
	gi 7290546	-----				
45	gi 1362625	-----				

Tables 2J-2EE list the domain descriptions from DOMAIN analysis results against NOV2a. This indicates that the NOV2a sequence has properties similar to those of other proteins known to contain this domain.

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Table 2J. Domain Analysis of NOV2a

gnl|Smart|smart00194, PTPc, Protein tyrosine phosphatase, catalytic domain (SEQ ID NO:93)
 CD-Length = 264 residues, 99.6% aligned
 Score = 318 bits (816), Expect = 2e-87

55

NOV 1:	1983	KFQEEFSELPK-FLQDLSSSTDADLPWNRANKRFPNIKPYNNNRVKLIADASVPGSDYINA	2041
		+ + + + ++ ++	
Sbjct:	1	GLEEEFEKLQRLTPDDLSC T VAILPENRDKNRYKDVL PYDHTRVKL-KPPPGEGSDYINA	59
NOV 1:	2042	SYISGYLCPNEFIATQGPLPGTVGDFWRMVWETRAKTLVMLTQCPEKGRIRCHQYWPEDN	2101

		+ + + + +	
	Sbjct:	60 SYIDGPNRPKAYIATQGGLPSTVEDFWRMVWEEKVPVIVMLTELVEKGREKCAQYWPEKE	119
5	NOV 1:	2102 KPVTVFGDIVITKLMEDVQIDWTIRDLEKIERHG--DCMTVRQCNTAWPEHGVPEPNSAPL	2159
		+ + + ++ + ++ + +	
	Sbjct:	120 GGSITYGDTITVTLKSVEKVDDYTITRTLEVTNTGGSETRTVTHYHYTNWPDHGVPEPNSAPL	179
	NOV 1:	2160 IHFVKLVASRAH--DTTPMIVHCSAGVGTGVFIALDHLTHQINDHDFVDIYGLVAELR	2217
10		+ + ++ ++ ++ + + + +	
	Sbjct:	180 LDLVRAVRKSQSTLRNSGPIVVHCSAGVGTGTGFIAIDILLQLEAGKEVDIFEIVKELR	239
	NOV 1:	2218 SERMCMVQNLAQYIFLHQCILDLL	2241
		+ ++ +	
15	Sbjct:	240 SQRPGMVQTEEQYIFLYRAILEYL	263

Table 2K. Domain Analysis of NOV2a

gnl|Pfam|pfam00102, Y_phosphatase, Protein-tyrosine phosphatase (SEQ ID NO:94)
CD-Length = 235 residues, 100.0% aligned
Score = 275 bits (704), Expect = 2e-74

	NOV 1:	2008 NRAKNRFPNIKPYNNNRVKLIADASVPGSDYINASYISGYLCPNEFIATQGGLPGTVGDF	2067
20		+ + ++ ++ + + +	
	Sbjct:	1 NKEKNRYKDVLPYDHTRVKL-KPLGDESDYINASYVDGYKKPKAYIATQGGLPNTIEDF	59
	NOV 1:	2068 WRMVWETRAKTLVMTQCFEKGRIRCHQYWPEDNKPVTVFGDI-VITKLMEDVQIDWTIR	2126
25		+ + + + + + + + + +	
	Sbjct:	60 WRMVWEEKVRVIVMLTELVEKGREKCAQYWPEKEGGSITYGDFTVTCVSVEKKDDYTVR	119
	NOV 1:	2127 DLKIERHGDC--MTVRQCNTAWPEHGVPEPNSAPLIHFVKLVASRAH-DTTPMIVHCSA	2183
		++ + ++ + + ++ ++ + ++	
	Sbjct:	120 TLELTNSGDDETRTVKHYHTGWPDHGVPEPNSAPLILDLRKVRKSKGTPDDGPIVVHCSA	179
30	NOV 1:	2184 GVGRTGVFIALDHLTHQINDHDFVDIYGLVAELRSERMCMVQNLAQYIFLHQCILD	2239
		+ + + ++ + + ++ +	
	Sbjct:	180 GIGRTGTGFIAIDILLQLEKEGVVDVFDTVKKLRSQRPGMVQTEEQYIFIYDAILE	235

Table 2L. Domain Analysis of NOV2a

gnl|Smart|smart00404, PTPc_motif, Protein tyrosine phosphatase, catalytic domain motif (SEQ ID NO:95)
CD-Length = 105 residues, 100.0% aligned
Score = 120 bits (301), Expect = 8e-28

35	NOV 1:	2138 TVRQCNTAWPEHGVPEPNSAPLIHFVKLVASRAH--DTTPMIVHCSAGVGTGVFIALD	2195
		+ ++ + + ++ ++ + ' + + + +	
	Sbjct:	1 TVKHYYHTGWPDHGVPEPNSAPLILEFLRAVKKSLNKSANNGPVVVHCSAGVGTGTGFVAID	60
40	NOV 1:	2196 HLTQHI-NDHDFVDIYGLVAELRSERMCMVQNLAQYIFLHQCILD	2239
		+ + + + + ++ + +	
	Sbjct:	61 ILLQLEAGTGEVDIFDIVKELRSQRPGAVQTLEQYLYRALLE	105

Table 2M. Domain Analysis of NOV2a

gnl|Pfam|pfam00041, fn3, Fibronectin type III domain (SEQ ID NO:96)
 CD-Length = 86 residues, 100.0% aligned
 Score = 60.8 bits (146), Expect = 8e-10

5
 NOV 1: 54 PGPPVFLAGERVGSAGILLSWNTPPNPNGRIISYIVKYKEVCPWMQTVYTQVRSKPDSLE 113
 | | | | | + | | | + | | | | | + | + | +
 Sbjct: 1 PSAPTNLTVTDVTSTSLTSLWSPPPDGNGPITGYEVEYQPVNS--GEEWNEITVPGTTTS 58
 NOV 1: 114 VLLTNLNPGETTYEIKVAAENSAGIGVFS 141
 | | | | | + + | | | | |
 Sbjct: 59 YTLTGLKPGTEYEVVRVQAVNGGGNGPPS 86

Table 2N. Domain Analysis of NOV2a

gnl|Pfam|pfam00041, fn3, Fibronectin type III domain (SEQ ID NO:96)
 CD-Length = 86 residues, 95.3% aligned
 Score = 58.9 bits (141), Expect = 3e-09

10
 NOV 1: 659 SSPQDVEVIDVTADEIRLKWSPPEKPNGIIAYEVLYKNIDTLYMKNT-----STTDIIL 713
 | + | + + | | | + + | | | | | | | | + + + | + | |
 Sbjct: 2 SAPTNLTVTDVTSTSLTSLWSPPPDGNGPITGYEVEYQPVNSGEEWNEITVPGTTTSYTL 61
 15
 NOV 1: 714 RNLRPHTLYNISVRSYTRFGHG 735
 | + | | | + | + + | + |
 Sbjct: 62 TGLKPGTEYEVVRVQAVNGGGNG 83

Table 2O. Domain Analysis of NOV2a

gnl|Pfam|pfam00041, fn3, Fibronectin type III domain (SEQ ID NO:96)
 CD-Length = 86 residues, 100.0% aligned
 Score = 57.0 bits (136), Expect = 1e-08

20
 NOV 1: 1330 PDVVQNMQCMATSWQSVLVKWDPPKKANGIITQYMTV-----ERNSTKVSPQDHMYT 1382
 | | + + + | + + | | | | | | | | | | | |
 Sbjct: 1 PSAPTNLTVTDVTSTSLTSLWSPPPDGNGPITGYEVEYQPVNSGEEWNEITVPGTTTSYT 60
 25
 NOV 1: 1383 FIKLLANTS YVFKVRASTSAGEGDES 1408
 | | | | | + | + | | | | | | | |
 Sbjct: 61 LTGLKPGTEYEVVRVQAVNGGGNGPPS 86

Table 2P. Domain Analysis of NOV2a

gnl|Pfam|pfam00041, fn3, Fibronectin type III domain (SEQ ID NO:96)
 CD-Length = 86 residues, 98.8% aligned
 Score = 53.1 bits (126), Expect = 2e-07

30
 NOV 1: 753 SAPENITYKNISSGEIELSFLPPSPNGIIQKYTIYLRKSNNGNE---ERTINTTSLTQNI 809
 | | | | + | + + + | + + | | | | + + | | | + + +
 Sbjct: 2 SAPTNLTVTDVTSTSLTSLWSPPPDGNGPITGYEVEYQPVNSGEEWNEITVPGTTTSYTL 61
 NOV 1: 810 KGLKKTQYIIIEVSASTLKKEGVRS 834
 | | | | + | + | | | | | | | |
 35
 Sbjct: 62 TGLKPGTEYEVVRVQAVNGGGNGPPS 86

Sbjct: 53 | + | | | + | | | |
 ---PGTTTSYTLTGLKPGTEYEVVRQAVNGGGNGPPS 86

Table 2U. Domain Analysis of NOV2a

gnl|Pfam|pfam00041, fn3, Fibronectin type III domain (SEQ ID NO:96)
 CD-Length = 86 residues, 98.8% aligned
 Score = 47.4 bits (111), Expect = 9e-06

5 NOV 1: 940 DPPKDVYYANLSSSSIIILFWTPPSKPNGIIQYYSVYYRNT-SGTFMQNFTLHEVTNDFDN 998
 | ++ +++|+|+ | |++| | | | | | + | | + |
 Sbjct: 2 SAPTNLTVTDVTSLSLTLWSPPPDGNGPITGYEVEYQPVNSGEEWNEITVPGTTT---- 57
 10 NOV 1: 999 MTVSTIIDKLTIFSYYTFWLTAHSVGNKNS 1030
 | + | + | + | | | | |
 Sbjct: 58 ---SYTLTGLKPGTEYEVVRQAVNGGGNGPPS 86

Table 2V. Domain Analysis of NOV2a

gnl|Pfam|pfam00041, fn3, Fibronectin type III domain (SEQ ID NO:96)
 CD-Length = 86 residues, 91.9% aligned
 Score = 47.0 bits (110), Expect = 1e-05

15 NOV 1: 1530 GPPENVHVVATSPFISISISWSEPAVITGP-TCYLIDVKSVDNDEFNISFIKSNEENKTIE 1588
 | | + | + |+++| | | | | | | + + + + | +
 Sbjct: 2 SAPTNLTVTDVTSLSLTLWSPPPDGNGPITGYEVEYQPVNSGEEWNEITVPGTTT-SYT 60
 NOV 1: 1589 IKDLEIFTRYSVVITAFTGN 1608
 + | + | | | + | |
 20 Sbjct: 61 LTGLKPGTEYEVVRQAVNGG 80

Table 2W. Domain Analysis of NOV2a

gnl|Pfam|pfam00041, fn3, Fibronectin type III domain (SEQ ID NO:96)
 CD-Length = 86 residues, 96.5% aligned
 Score = 46.6 bits (109), Expect = 2e-05

25 NOV 1: 1633 DPPNNMTFQKIPDEVTKFQLTFLPPSQPNNGIQVYQALVYREDDPTAVQIHNLSIIQKTN 1692
 | | + | + |++ | | | | | + + + +
 Sbjct: 2 SAPTNLTVTDVTS--TSLTLWSPPPDGNGPITGYEVEYQPVNSGEEWNEITVPGTTTS- 58
 NOV 1: 1693 TFVIAMLEGLKGGHTYINISVYAVNSAGAGP 1722
 | | | | | + | | | | |
 30 Sbjct: 59 -----YTTLTGLKPGTEYEVVRQAVNGGGNGP 84

Table 2X. Domain Analysis of NOV2a

gnl|Pfam|pfam00041, fn3, Fibronectin type III domain (SEQ ID NO:96)
 CD-Length = 86 residues, 98.8% aligned
 Score = 44.7 bits (104), Expect = 6e-05

NOV 1: 303 GPPQNCVTGNITGKSFSILWDPPTIVTGKFS-YRVELY---GPSAGRILDNSTKDLKFAF 358
 | | ++| ++ | | | + | | | + +
 Sbjct: 2 SAPTNLTVTDVTSLSLTLWSPPPDGNGPITGYEVEYQPVNSGEEWNEITVPGTTTSYTL 61

NOV 1: 359 TNLTPTFTMYDVYIAAETSAGTGPKS 383
 | | | | | + | | | |
 Sbjct: 62 TGLKPGTEYEVVRQAVNGGGNGPPS 86

5

Table 2Y. Domain Analysis of NOV2a

gnl|Pfam|pfam00041, fn3, Fibronectin type III domain (SEQ ID NO:96)
 CD-Length = 86 residues, 100.0% aligned
 Score = 43.1 bits (100), Expect = 2e-04

NOV 1: 561 PLSAQNFRVTHVTITEVFLHWDPDPVF--FHHYLITILDVENQSKSIILRTLNSLSLVL 618
 | + | | | | + | | | | + | + + + +
 Sbjct: 1 PSAPTNLTVTDVTSTSLTSLWSPPPDGNGPITGYEVEYQPVNSGEEWNEITVPGTTTSYT 60
 NOV 1: 619 I-GLKKYTKYKMRVAASTHVGESSL 643
 + | | | + | + | | | |
 Sbjct: 61 LTGLKPGTEYEVVRQAVNGGGNGPPS 86

10

Table 2Z. Domain Analysis of NOV2a

gnl|Pfam|pfam00041, fn3, Fibronectin type III domain (SEQ ID NO:96)
 CD-Length = 86 residues, 93.0% aligned
 Score = 38.5 bits (88), Expect = 0.004

NOV 1: 1047 VGNLTYESISSTAINVSWVPPAQPNGLVFYY-VSLILQQTPRHVRPPLVT-YERSIYFDN 1104
 | | | ++ | ++ + | | | | + | | + | |
 Sbjct: 4 PTNLTVTDVTSTSLTSLWSPPPDGNGPITGYEVEYQPVNSGEEWNEITVPGTTTSYTLTG 63
 NOV 1: 1105 LEKYTDYILKITPSTEGKFS 1124
 | + | + | + + + |
 Sbjct: 64 LKPGTEYEVVRQAVNGGGNG 83

15

20

Table 2AA. Domain Analysis of NOV2a

gnl|Smart|smart00060, FN3, Fibronectin type 3 domain; One of three
 types of internal repeat within the plasma protein, fibronectin. The
 tenth fibronectin type III repeat contains a RGD cell recognition
 sequence in a flexible loop between 2 strands. Type III modules are
 present in both extracellular and intracellular proteins. (SEQ ID
 NO:97)
 CD-Length = 83 residues, 96.4% aligned
 Score = 54.7 bits (130), Expect = 6e-08

NOV 1: 54 PGPPVFLAGERVGSAGILLSWNTPPNP-NGRIISYIVKYKEVCPWMQTVYTQVRSKPDSL 112
 | | | | | + | | | | + | + | + | + | +
 Sbjct: 1 PSPPSNLRVTDVTSTSVTLSEPPDDITGYIVGYRVEYREGEWKEVNVTP---SSTT 56
 NOV 1: 113 EVLLTNLNPGTTYEIKVAAENSAG 136
 | | | | | + | | |
 Sbjct: 57 SYTLTGLKPGTEYEFVRVANGEA 80

25

30

Table 2BB. Domain Analysis of NOV2a

gln|Smart|smart00060, FN3, Fibronectin type 3 domain; One of three types of internal repeat within the plasma protein, fibronectin. The tenth fibronectin type III repeat contains a RGD cell recognition sequence in a flexible loop between 2 strands. Type III modules are present in both extracellular and intracellular proteins. (SEQ ID NO:97)
CD-Length = 83 residues, 92.8% aligned
Score = 52.8 bits (125), Expect = 2e-07

5 NOV 1: 659 SSPQDVEVIDVTADEIRLKWSPPEKP-NGIIIIAYEVLYKNID---TLYMKNTSTTDIILR 714
| | ++ | ||| + + | | | | | + | | + + + || |
Sbjct: 2 SPPSNLRVIDVTSTSVTLSEPPPPDDITGYIVGYRVEYREEGEWKEVNVTPSSTTSYTLT 61
NOV 1: 715 NLRPHTLYNISVRSYTR 731
| + | | | +
Sbjct: 62 GLKPGTEYEFVRVAVNG 78

Table 2CC. Domain Analysis of NOV2a

gln|Smart|smart00060, FN3, Fibronectin type 3 domain; One of three types of internal repeat within the plasma protein, fibronectin. The tenth fibronectin type III repeat contains a RGD cell recognition sequence in a flexible loop between 2 strands. Type III modules are present in both extracellular and intracellular proteins. (SEQ ID NO:97)
CD-Length = 83 residues, 94.0% aligned
Score = 45.4 bits (106), Expect = 3e-05

10 NOV 1: 1235 PPQNLTLLINCTSDFVWLKWSPLPGGIVKVVSFKIHEHETDTIYYKNISGFKTEAKLVG 1294
| | | | + + | | | | | | + | + | | |
Sbjct: 3 PPSNLRVIDVTSTSVTLSEPPPPDDITGYIVGYRVEYREEGEWKEVNVTPSSTTSYTLTG 62
15 NOV 1: 1295 LEPVSTYSIRVSAFTKVG 1312
| + | + | | |
Sbjct: 63 LKPGTEYEFVRVAVNGEA 80

Table 2DD. Domain Analysis of NOV2a

gln|Smart|smart00060, FN3, Fibronectin type 3 domain; One of three types of internal repeat within the plasma protein, fibronectin. The tenth fibronectin type III repeat contains a RGD cell recognition sequence in a flexible loop between 2 strands. Type III modules are present in both extracellular and intracellular proteins. (SEQ ID NO:97)
CD-Length = 83 residues, 100.0% aligned
Score = 42.7 bits (99), Expect = 2e-04

20 NOV 1: 561 PLSAQNFRVTHVTITEVFLHWDPPDPVFFHHYLITILDVENQSKSIILRTLNS--LSLVL 618
| | | | | | | + | | + + ++ + + + | | |
Sbjct: 1 PPSNLRVIDVTSTSVTLSEPPPPDDITGYIVGYRVEYREEGEWKEVNVTPSSTTSYTL 60
25 NOV 1: 619 IGLKKYTKYKMRVAASTHVGESS 641
| | | | + | + | | |
Sbjct: 61 TGLKPGTEYEFVRVAVNGEAGEG 83

Table 2EE. Domain Analysis of NOV2a

gnl|Smart|smart00060, FN3, Fibronectin type 3 domain; One of three types of internal repeat within the plasma protein, fibronectin. The tenth fibronectin type III repeat contains a RGD cell recognition sequence in a flexible loop between 2 strands. Type III modules are present in both extracellular and intracellular proteins. (SEQ ID NO:97)
CD-Length = 83 residues, 92.8% aligned
Score = 41.2 bits (95), Expect = 7e-04

5 NOV 1: 848 SPPQDFSVKQLSGVTVKLSWQPPLEP-NGIILYYTVYVWRSS----LKTINVTETSLELS 902
Sbjct: 2 SPPSNLRVTDVTSTSVTLSEPPDDITGYIVGYRVEYREEGEWKEVNVTPSSTTSYTLT 61
NOV 1: 903 DLDYNVEYSAYVTASTR 919
Sbjct: 62 GLKPGTEYEFRVRAVNG 78

10 Receptor tyrosine phosphatases (rPTPs) are part of the signaling cascades that control cell survival, proliferation and differentiation. The novel protein tyrosine phosphatase described in the application contains a phosphatase domain and thirteen fibronectin type III repeats. It closely resembles rPTP-GMC1, a rat membrane phosphatase that is expressed in kidney glomerulus and is upregulated in response to kidney injury (Wright et.al. J Biol Chem

15 1998 Sep 11;273(37):23929-37). Tissue specificity of PTPs varies widely ; for eg rPTP-GMC1 is expressed by mesangial cells in the kidney while GLEPP1 (another membrane phosphatase) is expressed by podocytes in the kidney (Thomas et. al. ; J Biol Chem 1994 Aug 5;269(31):19953-62). Tappia et. al. demonstrated expression of a PTP in the liver could regulate the activity of the insulin and EGF receptors (Tappia et. al.; Biochem J 1993 May

20 15;292 (Pt 1):1-5).A number of phosphatases have been demonstrated to play a role in cancer, for eg. PTP zeta; a membrane phosphatase; is expressed in brain and is also expressed by a glioblastoma cell line (Krueger et. al.; Proc Natl Acad Sci U S A 1992 Aug 15;89(16):7417-21); rPTP alpha is expressed in breast tumors and correlates with tumor grade (Ardini et. al.; Oncogene 2000 Oct 12;19(43):4979-87). This phosphatase (rPTP alpha) is also expressed by

25 human prostate cancer cell lines, oral squamous cell carcinoma and was correlated with histological grade of the oral tumor (Zelivianski et. al.; Mol Cell Biochem 2000 May;208(1-2):11-8; Berndt et al.; Histochem Cell Biol 1999 May;111(5):399-403). PTP-1B has been suggested to play arole in diabetes and obesity (Kennedy et. al.; Biochem Pharmacol 2000 Oct 1;60(7):877-83) whle mutations in a PTP named EPM2A have been suggested as the

30 cause of Lafora's disease (and autosomal recessive form of progressive myoclonus epilepsy) (Minassian et. al. Nat Genet 1998 Oct;20(2):171-4). Given the wide ranging effects of this

family of proteins , we hypothesize that the novel protein described in this application plays a role in cancer, neurological, immune and metabolic diseases.

The disclosed NOV2 nucleic acid of the invention encoding a Protein tyrosine phosphatase precursor-like protein includes the nucleic acid whose sequence is provided in Table 2A, 2C, or 2E or a fragment thereof. The invention also includes a mutant or variant nucleic acid any of whose bases may be changed from the corresponding base shown in Table 2A, 2C, or 2E while still encoding a protein that maintains its Protein tyrosine phosphatase precursor like activities and physiological functions, or a fragment of such a nucleic acid. The invention further includes nucleic acids whose sequences are complementary to those just described, including nucleic acid fragments that are complementary to any of the nucleic acids just described. The invention additionally includes nucleic acids or nucleic acid fragments, or complements thereto, whose structures include chemical modifications. Such modifications include, by way of nonlimiting example, modified bases, and nucleic acids whose sugar phosphate backbones are modified or derivatized. These modifications are carried out at least in part to enhance the chemical stability of the modified nucleic acid, such that they may be used, for example, as antisense binding nucleic acids in therapeutic applications in a subject. In the mutant or variant nucleic acids, and their complements, up to about 16 percent of the bases may be so changed.

The disclosed NOV2 protein of the invention includes the Protein tyrosine phosphatase precursor-like protein whose sequence is provided in Table 2B, 2D, or 2F. The invention also includes a mutant or variant protein any of whose residues may be changed from the corresponding residue shown in Table 2B, 2D, or 2F while still encoding a protein that maintains its Protein tyrosine phosphatase precursor-like activities and physiological functions, or a functional fragment thereof. In the mutant or variant protein, up to about 18 percent of the residues may be so changed.

The invention further encompasses antibodies and antibody fragments, such as F_{ab} or $(F_{ab})_2$, that bind immunospecifically to any of the proteins of the invention.

The above defined information for this invention suggests that this Protein tyrosine phosphatase precursor-like protein (NOV2) may function as a member of a "Protein tyrosine phosphatase precursor family". Therefore, the NOV2 nucleic acids and proteins identified here may be useful in potential therapeutic applications implicated in (but not limited to) various pathologies and disorders as indicated below. The potential therapeutic applications for this invention include, but are not limited to: protein therapeutic, small molecule drug target, antibody target (therapeutic, diagnostic, drug targeting/cytotoxic antibody), diagnostic and/or

prognostic marker, gene therapy (gene delivery/gene ablation), research tools, tissue regeneration *in vivo* and *in vitro* of all tissues and cell types composing (but not limited to) those defined here.

The NOV2 nucleic acids and proteins of the invention are useful in potential
5 therapeutic applications implicated in cancer including but not limited to various pathologies and disorders as indicated below. For example, a cDNA encoding the Protein tyrosine phosphatase precursor-like protein (NOV2) may be useful in gene therapy, and the Protein tyrosine phosphatase precursor -like protein (NOV2) may be useful when administered to a subject in need thereof. By way of nonlimiting example, the compositions of the present
10 invention will have efficacy for treatment of patients suffering from cancer, kidney cancer, trauma, regeneration (in vitro and in vivo), viral/bacterial/parasitic infections, nephrological diseases including diabetes, autoimmune disease, renal artery stenosis, interstitial nephritis, glomerulonephritis, polycystic kidney disease, systemic lupus erythematosus, renal tubular acidosis, IgA nephropathy, hypercalcaemia, Lesch-Nyhan syndrome, Hirschsprung's disease ,
15 Crohn's Disease, appendicitis, or other pathologies or conditions. The NOV2 nucleic acid encoding the Protein tyrosine phosphatase precursor-like protein of the invention, or fragments thereof, may further be useful in diagnostic applications, wherein the presence or amount of the nucleic acid or the protein are to be assessed.

NOV2 nucleic acids and polypeptides are further useful in the generation of antibodies
20 that bind immuno-specifically to the novel NOV2 substances for use in therapeutic or diagnostic methods. These antibodies may be generated according to methods known in the art, using prediction from hydrophobicity charts, as described in the "Anti-NOVX Antibodies" section below. The disclosed NOV2 proteins have multiple hydrophilic regions, each of which can be used as an immunogen. In one embodiment, a contemplated NOV2 epitope is
25 from about amino acids 1 to 100. In another embodiment, a NOV2 epitope is from about amino acids 200 to 300. In further embodiments, a NOV2 epitope is from about amino acids 450 to 500, from about amino acids 600 to 900, from about amino acids 950 to 1000, from about amino acids 1200 to 1300, from about amino acids 1400 to 1600, from about amino acids 1800 to 1900, from about amino acids 1950 to 2050, and from about amino acids 2200 to
30 2300. These novel proteins can be used in assay systems for functional analysis of various human disorders, which will help in understanding of pathology of the disease and development of new drug targets for various disorders.

NOV3

A disclosed NOV3 nucleic acid of 4538 nucleotides (also referred to as 134899552_EXT) encoding a novel human homolog of the *Drosophila* pecanex-like protein is shown in Table 3A. An open reading frame was identified beginning with an ATG initiation codon at nucleotides 101-103 and ending with a TGA codon at nucleotides 4439-4441. A putative untranslated region upstream from the initiation codon and downstream from the termination codon is underlined in Table 3A, and the start and stop codons are in bold letters.

Table 3A. NOV3 nucleotide sequence (SEQ ID NO:11).

<p> CATGAAGGAAAAATCTGAGTATTCTAATGGCTTTTAAAAATAATCATTTATTTGCTAGGTAAGTTCTCTTC TACGCTGTATGAGACTGGTGGCTGTGATATGTCACCTTGTAATTTGAACCAGCAGCAAGAAGAGCATCCAA TATCTGGGACACAGATTCTCATGTATCCAGTTCTACCTCAGTTTCGATTTTATCCACATGATGTGATTTCGATT GAATAGACTATTGACCATTTGATACAGATTGTTGGAGCAACAGGACATTGATCTAAGCCCTGACTTGGCAGC TACTTACGGCCCAACAGAAGAAGCTGCCAAAAGGTTAAACACTATTATCGCTTTTGGATCCTACCCAGCT GTGGATTGGCATTAACTTTGACAGACTCACACTTTTGGCCCTGTTGATAGGAATCGTGAGATCCTGGAAAA TGTGTTAGCTGTCTCCTGGCTATTCTCGTGGCCTTTTGGGATCTATTCTCTCATACAAGGATTCTTCAG AGATATCTGGGTCTTCCAGTTCTGCCTCGTCTAGCCAGCTGTCAATACTCACTGCTTAAGAGTGTTCACCC AGATTTCTTCTTCCCAGACATGGTCTAATCGTATCATTGCCCTACAGTAGACCAGTTTATTTCTGCATATG TTGCGGTCTTATTGGCTCTTGATTATGGTAGCAAAACCTGACTGCAACCAAGTTCAAATATATGGAAT AACTTTACCAATCCACTGGTGTATATCAGCCAGGGATTAGTTATAGTGTTTACACTCTGTTTCCCAAT AGTGTTTTTCATTGGTCTCCTGCCTCAGGTGAATACATTTGTAATGTACCTTTGTGAACAATGGATATTCA TATTTTGGTGGTAATGCCACTACAAGCCTGCTTGACAGCACTTTACAGTTTATCTGTAGTGTGGCAGT AGCCTTATTTGTATGGATTATGTTATGGGGCTTTACAGGATTCTTGGGATGGCCAGCATATTCAGTACTTTT CTCCATTTTGTGGTGTATAGTGGCAGTGTCTTACCATCTCAGCCGACAAAGCAGTGATCCATCTGTAAT TAGCTCTTTAGTGCAATCCAAGATTTTCCAAAAACGGAAGAGAAAAATCCAGAAGACCCCTCTATCTGAAGT AAAAGATCCACTGCCTGAAAAACTTAGAAATCTGTTAGTGAGCGATTACAGTCTGACCTGGTAGTATGATG TGTAATTTGGTGTGCTGATTTTGTCTATTCTATGAAGCAGCTCTTCAAGTATTGCAGCCTGCCCTCAAGTA TGTGTTGTATACATTGGTTGGCTTTTGGGGTTTGTAAACCATATGTGCTGCCTCAAGTTAGAAAAACAGCT ACCATGGCAGTGTCTCTCATCCTCTGCTAAAGACACTAGAGTATAATCAGTATGAAGTTCCGATGTCAGC CACTATGTGGTGTGGTTTGAAGAACTTATGTTGGCTTCTTTTGTGGAGAAGAAATATAATCTATCCATTGAT TGTTCTCAATGAATGAGCAGCAGTGAGAGACAATTTGCTAGTCCAAAGAACTGAATACAGAGTTAGGTGC TTAATGATCACTGTGCTGGTTTGAAGTTGCTACGATCCTCTTTAGCAGCCCTACATATCAGTATGTTAC AGTCATCTTTACTGTGCTGTTTTTCAAATTTGACTATGAAGCTTTTTCAGAGACCATGCTGTTGGATCTCTT CTTTATGTCCATACTCTTCAACAAGCTTTGGGAAGTACTTTATAAATTCAGTGTGTGTATACCTATATTGC CCCATGGCAGATCAGATGGGGTCTGCTTTCCATGCTTTTGTCTCAGCCTTTTGCAGTGCCTCGTTTCAGCAT GCTGTTTATTAGGCTGCTGCTCGGCCCTTCTCTACTCCACTGAACCCCTTTCTGGGAAGTGCAATATT CATCATCTCATATGTCGACCTGTGAAATTTCTGGGAGAGAGACTATAGCACAAAACGAGTGGATCATTTAAA TACCAGATTGGCTTCCCAGCTTGATAGAAATCCAGGTTTCAGATGACAACAATCTGAATTCATCTTTTATGA GCATTTAACTAGATCCCTACAGCACAGCCTCTGTGGTGTATTTGCTACTAGGACGGTGGGGAACTACAGTAC AGGGGACTGTTTCATCCTTGCCCTGACTATCTCAATGCATTAGTACACCTTATAGAGATAGGCAATGGTCT GGTCACTTTTCAGCTGCGGGGACTTGAATTCAGAGGTACCTACTGTCAACAACGGGAAGTGGAGGCCATTAC TGAAGGTGTAGAGGAAGATGAAGGATTTTGCTGTTGTGAACCTGGCCATATTCCTCAGATGCTTTCATTTAA TGCTGCATTTAGCCAGCGATGGCTAGCTTGGGAAGTGATAGTCACAAAGTACATTCTGGAGGGTTATAGCAT CACTGATAACAGTGTGCTTCTATGCTTCAAGTCTTTGATCTTCGAAAGTACTCACCATTACTATGTCAA GGGTATCATTTATTTATGTTACGACCTCGTCTAAGCTAGAGGAGTGGCTAGCTAATGAGACAATGCAGGAAGG ACTTCGTCTGTGTGCTGATCGCAATTATGTGATGTGGACCCGACCTTTAATCCAAACATTGATGAAGACTA TGACCACCGACTGGCAGGCATATCTAGGGAGAGTTTCTGTGTGATTTACCTCAACTGGATAGAGTACTGCTC TTCCCGAAGAGCAAAGCCTGTGGATGTGGACAAGATTATCCCTAGTGACTCTCTGTTATGGACTCTGTGT TCTGGGACGGAGAGCTTTGGGGACTGCATCCCATCATATGTCCAGTAATTTAGAGTCACTCTCTATGGATT GCATGCCCTATTTAAAGGAGATTTCCGTATTTCTTCAATTCGAGATGAATGGATCTTTGCTGACATGGAATT GCTAAGAAAAGTAGTAGTCCCTGGGATCCGTATGTCCATTAACTTCATCAGGATCATTTTACTTCTCCAGA TGAGATGATGACCTACTGTGCTCTATGAAGCCATAGTATCTCATGAGAAGAACCTCGTAATGCCCATGA AGGGGACCTGCTAGGCGGAGTGCAGTACTTGCCAACCTCTCCCTCCTTGCTGTGCTCTGCGGCATGTCTGGA TGATGGCAACCAATGAATATAAAATCATCATGTCAACAGACGCTACCTGAGCTTCAGGGTCATTAAAGTGAA TAAGGAATGTGTCGAGGTCTTTGGGCAGGGCAACAGCAGGAGCTGTTTTTCTACGTAAACCGTAACCCAGA GAGAGGTAGCATCCAAAATGCAAGCAAGCCCTGAGAACAATGATAAACTCATCTTGATCAACTATTGG CTACCAATCTTTGTCTCACCCCTGACAACCTTCTACTCTGACAGCCACGAACAGCTTAAAGACATTCTTGG GGGTCTATCAGCTTGGGAAATATCAGGAACCTCATAGTGTCAACCTGGCAAGGCTTAGGAAAGGTTGCGG AGCTGGATGTAACAGTGGTGGCAATATTGAAGATTCTGATACTGGAGGTGGGACTTCTGCACTGGTAACAA </p>
--

TGCAACAACTGCCAACATCCCCACAGCAACGTGACCCAGGGAAGCATTGGAAATCCTGGGCAGGGATCAGG
AACTGGACTCCACCCACCTGTCACATCTTATCTCCAACACTAGGTACTAGCCACAGCTCTCACTCTGTGCA
GTCCGGGCTGGTCAGACAGTCTCTGCCCCGGGCTCAGTAGCCAGCCAGTCTTCTACTGTCTATAGCAGCCG
GCATTTCATCCCTCCGGATGTCCACCACTGGGTTGTGCCTTGTCCGGCTCTTCTACTAGTCAGATATCGCT
TCGAAACTTGCCATCATCCATCCCAATCCGACTGTGATGGTGAACCAATGGAACCCCTCAGGTCAGAGCGG
CCTGGCCTGTGTGCAGCAGGCTGCCTTCTCCAGCAGCTCCAGCCAAAGCATCCAGCCTGCAAAACATCA
CACTCTCGTGGGCTTTCTTGCAGCAGAGGAGGTGAGCAGTGCCTGATGCACAGCCAGGCAACACCTT
AAGTCTGCCAACAAATTCACACTCCAGAAAGCAGAAGTGAATTTACAGAGTCCAAATTTGTGGATCCCAATCA
AATTCTGGAAGGGATCAACCTGTCTAAAAGGAAAGAGCTACAGTGGCCTGATGAAGGAATCCGGTTAAAAGC
TGGGAGAAATAGCTGGAAGACTGGAGTCCGACAGGAGGCGATGGAAGGCCATGTGATTACCCGATGGGTGCC
TTGCAGCAGAGATCCAGGTACCAGATCCACATCGACAAGGCAGTGTCTTGGTCCAGATTGATGATAAATA
TGTGACTGTAATTGAAACTGGGGTACTAGAAGTGGGGCTGAAGTGTGAGCCAGTGTATTATATAAGACAT
TTCTTTTCCCTCTCAATCCAAGGCATTGGAAAAAGAGAGGAACAAGCAGAAGATGCCTGCAGGTATCACT
TT

The disclosed NOV3 nucleic acid sequence, localized to chromosome 14, has 2277 of 2283 bases (99%) identical to a gb:GENBANK-ID:AB018348|acc:AB018348.1 mRNA from *Homo sapiens* (*Homo sapiens* mRNA for KIAA0805 protein, partial cds) (E = 0.0).

5 A NOV3 polypeptide (SEQ ID NO:12) encoded by SEQ ID NO:11 has 1446 amino acid residues and is presented using the one-letter code in Table 3B. Signal P, Psort and/or Hydropathy results predict that NOV3 does not contain a signal peptide and is likely to be localized to the plasma membrane with a certainty of 0.8000. In other embodiments, NOV3 may also be localized to the mitochondrial inner membrane with a certainty of 0.4714, the 10 Golgi body with a certainty of 0.4000, or the endoplasmic reticulum (membrane) with a certainty of 0.3000.

Table 3B. Encoded NOV3 protein sequence (SEQ ID NO:12).

MSLVNFEPAARRASNIWDTDSHVSSSTSVRFYPHDVIRLNRLTIDTDLLEQQDIDLSPDLAATYGPTEEAA
QVKVHYFRWILPQLWIGINFDRLLTLLALFDRNREILENLAVILAILVAFGLSILLIQGFFRDIWVFQFCL
VIASCQYSLKSVQPDSSSPRHGHNRIIAYSRPVYFCICCGLIWLLDYGSRLTATKFKLYGIFTNPLVFI
SARDLVIVFTLCFPIVFFIGLLPQVNTFVMYLCEQLDIHIFGGNATTSLLAALYSFICSIVAVALLYGLCYG
ALQDSWDGQHIPVLFISIFCGLLVAVSYHLSRQSSDPSVLSLVQSKI FPKTEENPEDPLSEVKDPLPEKLR
NSVSERLQSDLVVCIVIGVLYFAIHVSTVFTVLQPALKYVLYTLVGFVGFVTHYVLPQVRKQLPWHCFSHPL
LKTLEYNQYEVDRDAATMMWFEEKLHVWLLFVEKNIIYPLIVLNLSSSAETIASPKKLNTELGAIMITVAGLK
LLRSSFSPTQYVTVI FTVLFFKFDYEAFTMLLDLFFMSILFNKLWELLYKLQFVYTYIAPWQITWGSA
FHAFAPFAVPRSAAMLFIQAAVSFAFFSTPLNPFLGSAIFITSYVRPVKFWERDYSTKRVDHSNTRLASQLDR
NPGSDDNNLSIFYEHLTRSLQHSLCGDLLLLGRWGNYSTGDCFILASDYLNALVHLIEIGNGLVTFQLRGLE
FRGTYCQOREVEAITEGVEEDEGFCCEPGHIPHMLSFNAAFSQRWLAWEVIVTKYILEGYSITDNSAASML
QVFDLRKVLTTYVYVKGI IYVTTSSKLEEWLANETMQEGLRLCADRNYVDVDPFNPINIDEDYDHLRAGISR
ESFCVIYLNWIEYCSSRRAPVDVDKSSSLVLCYGLCVLGRRALGTASHHMSNLESFLYGLHALFKGDFR
ISSIRDEWIFADMELLRKVVVPGIRMSIKLHQDHFTSPDEYDDPTVLYEATVSHEKNLVIAHEGDPAPWRSV
LANSPSLALRHVMDDGTNEYKIIMLNRRYLSFRVIKVNKECVRLWAGQQQELVFLNRNRPERSIQNAKQ
ALRNMINSSCDQPIGYPIFVSPLTTSYSDSHEQLKDI LGGPISLGNIRNFIVSTWHRLRKGCAGCNSGGNI
EDSDTGGGTSCTGNNATTANNPHSNVTQGSIGNPGQSGTGLHPPVTSYPPTLGTSHSSHVSQSLVRQSPA
RASVASQSSYCYSSRHSLSRMSTTGFPVPCRRSSTSQISLRNLPSSIQSRLSMVNQMEPSGQSLACVQHGLP
SSSSSSQSI PACKHHTLVGFLATEGGQSSATDAQPGNTLSPANNSHSRKAEVIYRVQIVDPSQILEGINLSK
RKELQWPDEGIRLKAGRNSWKDWSPEGMEGHVHRWVPCSRDPGRSHIDKAVLLVQIDDKYVTVIETGV
ELGAEV

15 The disclosed NOV3 amino acid sequence has 1355 of 1446 amino acid residues (93%) identical to, and 1409 of 1446 amino acid residues (97%) similar to, the 1446 amino

acid residue ptnr:SPTRMBL-ACC:Q9QYC1 protein from *Mus musculus* (Mouse)
(PECANEX 1) (E = 0.0).

NOV3 is expressed in at least Pancreas, Parathyroid Gland, Thyroid, Mammary
gland/Breast, Ovary, Placenta, Uterus, Colon, Liver, Bone Marrow, Lymphoid tissue, Spleen,
5 Tonsils, Prostate, Testis, Brain, Lung, and Kidney . This information was derived by
determining the tissue sources of the sequences that were included in the invention including
but not limited to SeqCalling sources, Public EST sources, Literature sources, and/or RACE
sources.

In addition, NOV3 is predicted to be expressed in *Homo sapiens* heart, melanocyte, B-
10 cells, larynx, skin, CNS, and multiple sclerosis lesions because of the expression pattern of the
following sequences (which are publicly available ESTS for the sequence of the invention)
AB018348, BE881203, BE867469, BE867415, AB007895, NM_014801, U74315,
BE880986, W500099, AW250617, AA426168, AW246742, AA284182, W46420,
H14491, Z44921, BE930588, AI922381, AI215559, AA923742, AA582883, BE797814,
15 N75143, BE049421, F07632, BE797239, AI168579, AV653955, BE065657, AL079849,
and BE767656, closely related *Homo sapiens* mRNA for KIAA proteins, partial cds homolog.

NOV3 also has homology to the amino acid sequences shown in the BLASTP data
listed in Table 3C.

0

Table 3C. BLAST results for NOV3					
Gene Index/ Identifier	Protein/ Organism	Length (aa)	Identity (%)	Positives (%)	Expect
ref XP_027243.1 (XM_027243)	hypothetical protein XP_027243 [Homo sapiens]	619	619/619 (100%)	619/619 (100%)	0.0
gi 15076843 gb AAK8 2958.1 AF233450_1 (AF233450)	pecanex-like protein 1 [Homo sapiens]	2341	1372/1451 (94%)	1376/1451 (94%)	0.0
gi 6650377 gb AAF21 809.1 AF096286_1 (AF096286)	pecanex 1 [Mus musculus]	1446	1296/1446 (89%)	1344/1446 (92%)	0.0
gi 13171105 gb AAK1 3590.1 AF154413_1 (AF154413)	pecanex [Takifugu rubripes]	1703	1079/1466 (73%)	1204/1466 (81%)	0.0
gi 7290294 gb AAF45 755.1 (AE003423)	pcx gene product [alt 1] [Drosophila melanogaster]	3437	320/554 (57%)	424/554 (75%)	0.0

20

The homology of these sequences is shown graphically in the ClustalW analysis shown in Table 3D.

Table 3D. ClustalW Analysis of NOV3

5 1) NOV3 (SEQ ID NO:12)
2) ref|XP_027243.1| (XM_027243) hypothetical protein XP_027243 [Homo sapiens] (SEQ ID NO:42)
3) gi|15076843|gb|AAK82958.1|AF233450_1 (AF233450) pecanex-like protein 1 [Homo sapiens] (SEQ ID NO:43)
10 4) gi|6650377|gb|AAF21809.1|AF096286_1 (AF096286) pecanex 1 [Mus musculus] (SEQ ID NO:44)
5) gi|13171105|gb|AAK13590.1|AF154413_1 (AF154413) pecanex [Takifugu rubripes] (SEQ ID NO:45)
15 6) gi|7290294|gb|AAF45755.1| (AE003423) pcx gene product [alt 1] [Drosophila melanogaster] (SEQ ID NO:46)

20 NOV3
ref|XP_027243.1
gi|15076843|gb| MGSQTLQILRQGVAAALSGGWYYDPHQATFVNALHLYLWLFLLGLPFTLYMALPSTMIIV 1
gi|6650377|gb|A ----- 1
gi|13171105|gb| MGSQTLQILRQGVASVTGGWYYDPDQNTFVNALHLYIWLFLLCFPFTLYMALQPSMVIV 60
gi|7290294|gb|A ----- 1

25 NOV3
ref|XP_027243.1
gi|15076843|gb| AVYCPVIAAVFIVLKMVNYRLHRLDAGEVVDRTANEFTDQR-TKAEQGNCSRRKDSNG 119
gi|6650377|gb|A ----- 1
gi|13171105|gb| GIYCGVIAAMFLLKTVNYRLHHLALDEGEVVEHQTRSKSGRGGTGGANDPVTRREDSNG 120
gi|7290294|gb|A ----- 1

30 NOV3
ref|XP_027243.1
gi|15076843|gb| PSDPGGGIEMSEFIREATPPVGCSSRNSYAGLDPSNQIGSGSSRLGTAATIKGDTDTAKT 179
gi|6650377|gb|A ----- 1
gi|13171105|gb| LGDPGGGIEMADFIHQETPPVDCSSRNSYVG----- 151
gi|7290294|gb|A ----- 1

35 NOV3
ref|XP_027243.1
gi|15076843|gb| SDDISLSLGQSSSLCKEGSEEQDLAADRKLFRLVSNDSFISIQPSLSSCGQDLPRDFSDK 239
gi|6650377|gb|A ----- 1
gi|13171105|gb| ----- 151
gi|7290294|gb|A ----- 1

40 NOV3
ref|XP_027243.1
gi|15076843|gb| VNLPSHNNHHHVDQSLSSACDTEVASLVPLHSHSYRKDHRPRGVPTSSSAVAFPDTSLN 299
gi|6650377|gb|A ----- 1
gi|13171105|gb| ----- 151
gi|7290294|gb|A ----- 1

45 NOV3
ref|XP_027243.1
gi|15076843|gb| ----- 1
gi|6650377|gb|A ----- 1
gi|13171105|gb| ----- 151
gi|7290294|gb|A ----- 1

50 NOV3
ref|XP_027243.1
gi|15076843|gb| ----- 1
gi|6650377|gb|A ----- 1
gi|13171105|gb| ----- 151
gi|7290294|gb|A ----- 1

55 NOV3
ref|XP_027243.1
gi|15076843|gb| ----- 1
gi|6650377|gb|A ----- 1
gi|13171105|gb| ----- 151
gi|7290294|gb|A ----- 1

60 NOV3
ref|XP_027243.1
gi|15076843|gb| ----- 1
gi|6650377|gb|A ----- 1
gi|13171105|gb| ----- 151
gi|7290294|gb|A ----- 1

65 NOV3
ref|XP_027243.1
gi|15076843|gb| ----- 1
gi|6650377|gb|A ----- 1
gi|13171105|gb| ----- 151
gi|7290294|gb|A ----- 1

gi|15076843|gb|DFPLYQRRGLDPVSELESSKPLSGSKESLVENSGLSGEFQLAGDLKINTSQPPTKSGKS 359
 gi|6650377|gb|A-----1
 gi|13171105|gb|-----151
 gi|7290294|gb|A-----1

5

370 380 390 400 410 420
|....|....|....|....|....|....|....|....|....|....|....|
 -----1
 NOV3
 ref|XP_027243.1-----1
 gi|15076843|gb|KPLKAEEKSMDLSRLSLSTRSSGSTESYCSGTDRTNSTVSSYKSEQTSSTHIESILSEHEE 419
 gi|6650377|gb|A-----1
 gi|13171105|gb|-----MDL 154
 gi|7290294|gb|A-----1

10

430 440 450 460 470 480
|....|....|....|....|....|....|....|....|....|....|....|
 -----1
 NOV3
 ref|XP_027243.1-----1
 gi|15076843|gb|SPKAGTKSGRKKECCAGPEEKNSCASKRTSSEKIAMEASTNSGVHEAKDPTSPDEMHNQ 479
 gi|6650377|gb|A-----1
 gi|13171105|gb|NQRMSSSTHGRTTVAKAPG-----172
 gi|7290294|gb|A-----1

15

490 500 510 520 530 540
|....|....|....|....|....|....|....|....|....|....|....|
 -----1
 NOV3
 ref|XP_027243.1-----1
 gi|15076843|gb|RGLSTSASEEANKNPHANEFTSQGDRPPGNTAENKEEKSDKSAVSVDSKVRKDVGGKQKE 539
 gi|6650377|gb|A-----1
 gi|13171105|gb|-----172
 gi|7290294|gb|A-----1

20

550 560 570 580 590 600
|....|....|....|....|....|....|....|....|....|....|....|
 -----1
 NOV3
 ref|XP_027243.1-----1
 gi|15076843|gb|GDVRPKSSSVIHRTASAHKSGRRRTGKKRASSFDSSRHRDYVCFRGVSGTKPHSAIFCHD 599
 gi|6650377|gb|A-----1
 gi|13171105|gb|-----S-----173
 gi|7290294|gb|A-----1

35

610 620 630 640 650 660
|....|....|....|....|....|....|....|....|....|....|....|
 -----1
 NOV3
 ref|XP_027243.1-----1
 gi|15076843|gb|EDSSDQSDLSRASSVQSAHQFSSDSSSSTTSHSCQSPGGRYSALKTKHTHKERTDSEHT 659
 gi|6650377|gb|A-----1
 gi|13171105|gb|-----173
 gi|7290294|gb|A-----1

45

670 680 690 700 710 720
|....|....|....|....|....|....|....|....|....|....|....|
 -----1
 NOV3
 ref|XP_027243.1-----1
 gi|15076843|gb|HKAHLVPEGTSKKRATRTSSTNSAKTRARVLSLDSGTVACLNDSNRLMAPESIKPLTTS 719
 gi|6650377|gb|A-----1
 gi|13171105|gb|-----173
 gi|7290294|gb|A-----1

55

730 740 750 760 770 780
|....|....|....|....|....|....|....|....|....|....|....|
 -----1
 NOV3
 ref|XP_027243.1-----1
 gi|15076843|gb|KSDLEAKEGEVLDELSELLGRASQLETVTRSRNSLPNQVAFPEGEEQDAVSGAAQASEEAV 779
 gi|6650377|gb|A-----1
 gi|13171105|gb|-----EETV 177
 gi|7290294|gb|A-----1

60

790 800 810 820 830 840
|....|....|....|....|....|....|....|....|....|....|....|
 -----1

65

70

5	NOV3 ref XP_027243.1 gi 15076843 gb gi 6650377 gb A gi 13171105 gb gi 7290294 gb A	----- SFRERSTFRQAVRRRHNAGSNPTPTLLIGSPLSLQDGGQQQSTAQ-----VKVQS IFRRERSTFRQAVRRRHNAGSNPTPTSLIGSPLRYALHEADRPSGVRSWYRTVKSQPS -----	1 1 833 1 237 1
10	NOV3 ref XP_027243.1 gi 15076843 gb gi 6650377 gb A gi 13171105 gb gi 7290294 gb A	850 860 870 880 890 900 RPPSQAAVLASASALLVRNGSVHLEASHDNASAVGGSSLHDELGKFSSTLYETGGCDMSL RTPSQVTVLSTSASLLARNGSTHLEGSQDKASTVGTSTLQDEFGTLTPSLYEIRGCHTGL -----	3 1 893 3 297 1
20	NOV3 ref XP_027243.1 gi 15076843 gb gi 6650377 gb A gi 13171105 gb gi 7290294 gb A	910 920 930 940 950 960 VNFEPAARRASN-IWDTDSHVSSSTSVRFYPHDVI-----LNRLLLTIDTDLLEQQDIDL VNFEPAARRASN-ICDTDSHVSSSTSVRFYPHDVLSLPQIRLNRLLLTIDTDLLEQQDIDL VNFEPAARRASN-ICDTDSHVSSSTSVRFYPHDMIR-----LNRLLLTIDTDLLEQQDIDL GNFESATRRASNNIWDTDSHLSSTSVRFYPHDLISLHHIRANRLLTMDPELLEQQD-DL -----	57 1 952 57 356 1
30	NOV3 ref XP_027243.1 gi 15076843 gb gi 6650377 gb A gi 13171105 gb gi 7290294 gb A	970 980 990 1000 1010 1020 SPDLAAT-----YGPTEBAACKVKHYRFWILPOLWIGINFDRLTLLALFDRNREILENV SPDLAAT-----YGPTEBAACKVKHYRFWILPOLWIGINFDRLTLLALFDRNREILENV SPDLAAT-----YGPTEBAACKVKHYRFWILPOLWIGINFDRLTLLALFDRNREILENV SPDLQDAPLGQDNPSAASAAGKTQYYRWILPFLWVGLHFDRLTLLALFDRNREILENV -----	112 1 1007 112 416 1
40	NOV3 ref XP_027243.1 gi 15076843 gb gi 6650377 gb A gi 13171105 gb gi 7290294 gb A	1030 1040 1050 1060 1070 1080 LAVILAILVAFLGSIILLIQGFFRDIWVFQCLVIASCOYSLLSKVQPDSSSPRHGHNRII LAVILAILVAFLGSIILLIQGFFRDIWVFQCLVIASCOYSLLSKVQPDSSSPRHGHNRII LAVILAILVAFLGSIILLIQGFFRDIWVFQCLVIASCOYSLLSKVQPDSSSPRHGHNRII LAVILAILVAFLGSIILLIQGFFRDIWVFQCLVIASCOYSLLSKVQPDSSSPRHGHNRII -----	172 1 1067 172 476 1
50	NOV3 ref XP_027243.1 gi 15076843 gb gi 6650377 gb A gi 13171105 gb gi 7290294 gb A	1090 1100 1110 1120 1130 1140 AYSRPVYFCICCGLIWLLDYGSRNLTATKFKLYGTFITNPLVFIISARDLVIVFTLCFPII AYSRPVYFCICCGLIWLLDYGSRNLTATKFKLYGTFITNPLVFIISARDLVIVFTLCFPII AYSRPVYFCICCGLIWLLDYGSRNLTATKFKLYGTFITNPLVFIISARDLVIVFTLCFPII AYSRPVYFCICCGLIWLLDYGSRNLTATKFKLYGTFITNPLVFIISARDLVIVFTLCFPII -----	232 1 1127 232 536 1
60	NOV3 ref XP_027243.1 gi 15076843 gb gi 6650377 gb A gi 13171105 gb gi 7290294 gb A	1150 1160 1170 1180 1190 1200 FFIGLLPQVNTFVMYLCEQLDIHIFGGNATSLLAALYSFHCISIVAVALLYGLCYGALQD FFIGLLPQVNTFVMYLCEQLDIHIFGGNATSLLAALYSFHCISIVAVALLYGLCYGALKD FFIGLLPQVNTFVMYLCEQLDIHIFGGNATSLLAALYSFHCISIVAVALLYGLCYGALRD FFIGLLPQVNTFVMYLCEQLDIHIFGGNATSLLAALYSFHCISIVAVALLYGLCYGALKD -----	292 1 1187 292 596 1
70	NOV3 ref XP_027243.1 gi 15076843 gb gi 6650377 gb A gi 13171105 gb gi 7290294 gb A	1210 1220 1230 1240 1250 1260 SWDGOHIVPVLFSIFCGLLVAVSYHLSRQSDPSVLSIVOSKIFPKTEBKNPEDPLSEVK SWDGOHIVPVLFSIFCGLLVAVSYHLSRQSDPSVLSIVOSKIFPKTEBKNPEDPLSEVK SWDGOHIVPVLFSIFCGLLVAVSYHLSRQSDPSVLSIVOSKIFPKTEBKNPEDPLSEVK SWDGOHIVPVLFSIFCGLLVAVSYHLSRQSDPSVLSIVOSKIFPKTEBKNPEDPLSEVK -----	352 1 1247 352 656 1

gi|7290294|gb|A VVG-----NEGQ-----VMLRAKRSDLVNNKRLKMMV 131

1750 1760 1770 1780 1790 1800

5 NOV3
ref|XP_027243.1
gi|15076843|gb|
gi|6650377|gb|A
gi|13171105|gb|
gi|7290294|gb|A

RLCADRNYVDVDPFTFNPNIDEDYDHRLAGISRESFCVIYLNWIEYCSSRRRAKPVVDVKD 891
RLCADRNYVDVDPFTFNPNIDEDYDHRLAGISRESFCVIYLNWIEYCSSRRRAKPVVDVKD 64
RLCADRNYVDVDPFTFNPNIDEDYDHRLAGISRESFCVIYLNWIEYCSSRRRAKPVVDVKD 1786
RLCADRNYVDVDPFTFNPNIDEDYDHRLAGISRESFCVIYLSWIEYCSSRRRAKPLVDVKD 891
RGCSERNYVDLDAFTFNPNIDEDYDHRLSGISRSDFCGVYLGWICYCNSRRKPLDSEKD 1195
RRKPPDQRVFVVVGGGPSGAVAVETIROEGFGRGLIFVCREDTLPYDRVKISKAMNLEIE 191

1810 1820 1830 1840 1850 1860

15 NOV3
ref|XP_027243.1
gi|15076843|gb|
gi|6650377|gb|A
gi|13171105|gb|
gi|7290294|gb|A

SSLVTLCYGLCVLGRRAALGTASHHSSNLESFLYGLHALFKGDFRISIRDEWIFADMEL 951
SSLVTLCYGLCVLGRRAALGTASHHSSNLESFLYGLHALFKGDFRISIRDEWIFADMEL 124
SSLVTLCYGLCVLGRRAALGTASHHSSNLESFLYGLHALFKGDFRISIRDEWIFADMEL 1846
SSLVTLCYGLCVLGRRAALGTASHHSSNLESFLYGLHALFKGDFRISIRDEWIFADMEL 951
SALVLLCFGLCVLGRRAALGTAAHQMSSNLESFLYGLHALFKGDFRISIRDEWIFADMEL 1255
Q-----LRFR-----DEEFYKEYDIELVQGVAAEKLDTAQKELHCSNGYVVKYDKI 237

1870 1880 1890 1900 1910 1920

25 NOV3
ref|XP_027243.1
gi|15076843|gb|
gi|6650377|gb|A
gi|13171105|gb|
gi|7290294|gb|A

LRKVVPGIRMSIK-LHQDHFTSPDEYDDPTVLYEAIVSHEKNLVIAHEGDPAPWRSAVLA 1010
LRKVVPGIRMSIK-LHQDHFTSPDEYDDPTVLYEAIVSHEKNLVIAHEGDPAPWRSAVLA 183
LRKVVPGIRMSIK-LHQDHFTSPDEYDDPTVLYEAIVSHEKNLVIAHEGDPAPWRSAVLA 1905
LRKVVPGIRMSIK-LHQDHFTSPDEYDDPTVLYEAIVSHEKNLVIAHEGDPAPWRSAVLA 1010
LRKVVPGIRMSIK-LHQDHFTSPDEYDDPTVLYEAIVSHEKNLVIAHEGDPAPWRSAVLA 1314
YLATGCSAFPPPGVNLNVRVRELAETKAILASITPESV-----VVC 282

1930 1940 1950 1960 1970 1980

30 NOV3
ref|XP_027243.1
gi|15076843|gb|
gi|6650377|gb|A
gi|13171105|gb|
gi|7290294|gb|A

NSPSLLALRHVMDDGTNEYKIIIMLNRRYLSFRVIKVNKECVRLWAGQQQELVFLNRNP 1070
NSPSLLALRHVMDDGTNEYKIIIMLNRRYLSFRVIKVNKECVRLWAGQQQELVFLNRNP 243
NSPSLLALRHVMDDGTNEYKIIIMLNRRYLSFRVIKVNKECVRLWAGQQQELVFLNRNP 1965
NSPSLLALRHVMDDGTNEYKIIIMLNRRYLSFRVIKVNKECVRLWAGQQQELVFLNRNP 1070
NAPSLLALRHVMDDGTNEYKIIIMLNRRYLSFRVIKVNKECVRLWAGQQQELVFLNRNP 1374
LGSSFTALEAAAGLVSKVQSVTVVVGRENMPKAAFGAFIGORVLLQLFEDNKVMMRMESG- 341

1990 2000 2010 2020 2030 2040

40 NOV3
ref|XP_027243.1
gi|15076843|gb|
gi|6650377|gb|A
gi|13171105|gb|
gi|7290294|gb|A

ERGSIQNAKQALRNMINSSCDQPIGYPIFVSPLTTSYSDSHQKDLGGPISLGNIRNF 1130
ERGSIQNAKQALRNMINSSCDQPIGYPIFVSPLTTSYSDSHQKDLGGPISLGNIRNF 303
ERGSIQNAKQALRNMINSSCDQPIGYPIFVSPLTTSYSDSHQKDLGGPISLGNIRNF 2025
ERGSIQNAKQALRNMINSSCDQPIGYPIFVSPLTTSYSDSHQKDLGGPISLGNIRNF 1130
ERGSIQNAKQALRNMINSSCDQPIGYPIFVSPLTTSYCNHSPOLRHILGGPISFCNIRNF 1434
-IABIVGNEDGKVSFVWLVDTRIPCDLILGTGSKLNTQFLAKSGVKVNRNGSVVDVTF 400

2050 2060 2070 2080 2090 2100

50 NOV3
ref|XP_027243.1
gi|15076843|gb|
gi|6650377|gb|A
gi|13171105|gb|
gi|7290294|gb|A

IVSTWHRLRKCCGAGCNSGGNIEDSDTGGGTSCIGNNATTANNPHSNVTQGSICNPGQGS 1190
IVSTWHRLRKCCGAGCNSGGNIEDSDTGGGTSCIGNNATTANNPHSNVTQGSICNPGQGS 363
IVSTWHRLRKCCGAGCNSGGNIEDSDTGGGTSCIGNNATTANNPHSNVTQGSICNPGQGS 2085
IVSTWHRLRKCCGAGCNSGGNIEDSDTGGGTSCPGNSAVTASDPHNNVSOGSTGHPGQGA 1190
VVSTWHRLRKCCGAGCNSGGNIEDSDAGC----- 1463
HBS--N-MP-----DVYVGGDIANAHIHC----- 421

2110 2120 2130 2140 2150 2160

60 NOV3
ref|XP_027243.1
gi|15076843|gb|
gi|6650377|gb|A
gi|13171105|gb|
gi|7290294|gb|A

GTGLHPPVTSYPPTLGTSHSSHVSQSLVRQSPARASVASQSS-YCYSS-RHSSLRMSTT 1248
GTGLHPPVTSYPPTLGTSHSSHVSQSLVRQSPARASVASQSS-YCYSS-RHSSLRMSTT 421
GTGLHPPVTSYPPTLGTSHSSHVSQSLVRQSPARASVASQSS-YCYSS-RHSSLRMSTT 2143
GTGLHPPVTSYPPTLGTSHSSHVSQSLVRQSPARASVASQSS-YCYSS-RHSSLRMSTT 1248
-----LS-CGTSSSSQSVQSLVRHSPARASVSQSSVRYSSSRHSSLRITTT 1511
-----LAHDRVNIIGHYQIAQYHGRVAINMCG----- 448

2170 2180 2190 2200 2210 2220

70 NOV3
ref|XP_027243.1
gi|15076843|gb|

GFVPCRRSSTSQISLRNLPSSIQSRLSMVNQMEPSGQSGIACVQHGLPSSSSSSQSIPAC 1308
GFVPCRRSSTSQISLRNLPSSIQSRLSMVNQMEPSGQSGIACVQHGLPSSSSSSQSIPAC 481
GFVPCRRSSTSQISLRNLPSSIQSRLSMVNQMEPSGQSGIACVQHGLPSSSSSSQSIPAC 2203

	gi 6650377 gb A	GFVPCRRSSTSQISLRNLPSSIQSRLSMVNQMEARSQCGVGCVOHGLPSSSSSSQSIPAC	1308
	gi 13171105 gb	GLEPCRRSSTSQISLRNLPSSIQSRLSMVNQMEARSQCGVGCVOHGLPSSSSSSQSIPAC	1558
	gi 7290294 gb A	--G-----VKKLEAVPFFFTLIFGKG--RYAG-----HG--SYKDVIIDGSM	485
5		2230 2240 2250 2260 2270 2280	
	NOV3	KHHTLVGFLATEGGQSSATDAQ-----PGNTLSPANNSHS--RKAEEVIYRVQIVDPSQIL	1361
	ref XP_027243.1	KHHTLVGFLATEGGQSSATDAQ-----PGNTLSPANNSHS--RKAEEVIYRVQIVDPSQIL	534
10	gi 15076843 gb	KHHTLVGFLATEGGQSSATDAQ-----PGNTLSPANNSHS--RKAEEVIYRVQIVDPSQIL	2256
	gi 6650377 gb A	KHHTLVAFGLAEGGQSSATDAQ-----PGNTLSPANNISHA--RKAEEVIYRVQIVDPSQIL	1361
	gi 13171105 gb	KRHTLVGLLGNDCLCSTVTPPLSQHHHPHHHPQQHNPHTATVRRDDISYRVQIVDVGQVL	1618
	gi 7290294 gb A	EDFKFVAMFINDADTVIVASC-----G-----RQPIVAQFAELISQKCL	526
15		2290 2300 2310 2320 2330 2340	
	NOV3	EGINLSKRKELQWPDEGIRLKAGRNSWKDWSPOEGMEGHVHRWVPCSRDPGTRSHIDKA	1421
	ref XP_027243.1	EGINLSKRKELQWPDEGIRLKAGRNSWKDWSPOEGMEGHVHRWVPCSRDPGTRSHIDKA	594
	gi 15076843 gb	EGINLSKRKELQWPDEGIRLKAGRNSWKDWSPOEGMEGHVHRWVPCSRDPGTRSHIDKA	2316
20	gi 6650377 gb A	EGINLSKRKELQWPDEGIRLKAGRNSWKDWSPOEGMEGHVHRWVPCSRDPGTRSHIDKA	1421
	gi 13171105 gb	ENINLSKRKELQWPDDAMRHKAGRTQWRDWSPLEGMEGHVHRWVPCSRDPGSRSHIDKT	1678
	gi 7290294 gb A	G-----RGQIEDP-----A-----IREDWTKKLCQP-----LPQVR-----	552
25		2350 2360	
	NOV3	VLLVQIDDKYVTIETGVLELGAEV	1446
	ref XP_027243.1	VLLVQIDDKYVTIETGVLELGAEV	619
	gi 15076843 gb	VLLVQIDDKYVTIETGVLELGAEV	2341
	gi 6650377 gb A	VLLVQIDDKYVTIETGVLELGAEV	1446
	gi 13171105 gb	VLLVQVEDKTVPIETGVLELGAEV	1703
30	gi 7290294 gb A	-----	552

Pecanex gene was originally discovered in *Drosophila*, encoding a large, membrane-spanning protein. The mouse homolog was recently reported. In the absence of maternal expression of the pecanex gene, the embryo develops severe hyperneuralization similar to that characteristic of Notch mutant embryos. Early gastrula embryos, lacking both maternally and zygotically expressed activity of the neurogenic pecanex locus, are shown to contain a greater than wild-type number of stably determined neural precursor cells which can differentiate into neurons in culture. Therefore it is anticipated that this novel human pecanex will be involved in neuronal differentiation, maintenance of neuronal precursors and neurological diseases.

The disclosed NOV3 nucleic acid of the invention encoding a Human homolog of the *Drosophila* pecanex protein includes the nucleic acid whose sequence is provided in Table 3A or a fragment thereof. The invention also includes a mutant or variant nucleic acid any of whose bases may be changed from the corresponding base shown in Table 3A while still encoding a protein that maintains its Human homolog of the *Drosophila* pecanex activities and physiological functions, or a fragment of such a nucleic acid. The invention further includes nucleic acids whose sequences are complementary to those just described, including nucleic acid fragments that are complementary to any of the nucleic acids just described. The invention additionally includes nucleic acids or nucleic acid fragments, or complements thereto, whose structures include chemical modifications. Such modifications include, by way

of nonlimiting example, modified bases, and nucleic acids whose sugar phosphate backbones are modified or derivatized. These modifications are carried out at least in part to enhance the chemical stability of the modified nucleic acid, such that they may be used, for example, as antisense binding nucleic acids in therapeutic applications in a subject. In the mutant or variant nucleic acids, and their complements, up to about 1 percent of the bases may be so changed.

The disclosed NOV3 protein of the invention includes the Human homolog of the *Drosophila* pecanex protein whose sequence is provided in Table 3B. The invention also includes a mutant or variant protein any of whose residues may be changed from the corresponding residue shown in Table 3B while still encoding a protein that maintains its Human homolog of the *Drosophila* pecanex activities and physiological functions, or a functional fragment thereof. In the mutant or variant protein, up to about 7 percent of the residues may be so changed.

The NOV3 nucleic acids and proteins of the invention are useful in potential therapeutic applications implicated in cancer, trauma, regeneration (in vitro and in vivo), viral/bacterial/parasitic infections, cardiomyopathy, atherosclerosis, hypertension, congenital heart defects, aortic stenosis, atrial septal defect (ASD), atrioventricular (A-V) canal defect, ductus arteriosus, pulmonary stenosis, subaortic stenosis, ventricular septal defect (VSD), valve diseases, tuberous sclerosis, multiple sclerosis, scleroderma, obesity, endometriosis, fertility, hypercoagulation, autoimmune disease, allergies, immunodeficiencies, transplantation, hemophilia, idiopathic thrombocytopenic purpura, graft versus host disease, Von Hippel-Lindau (VHL) syndrome, Alzheimer's disease, stroke, hypercalcaemia, Parkinson's disease, Huntington's disease, cerebral palsy, epilepsy, ataxia-telangiectasia, leukodystrophies, behavioral disorders, addiction, anxiety, pain, neuroprotection, systemic lupus erythematosus, asthma, emphysema, ARDS, laryngitis, psoriasis, actinic keratosis, acne, hair growth/loss, alopecia, pigmentation disorders, endocrine disorders, diabetes, renal artery stenosis, interstitial nephritis, glomerulonephritis, polycystic kidney disease, systemic lupus erythematosus, renal tubular acidosis, IgA nephropathy, Lesch-Nyhan syndrome, and a variety of kidney diseases and/or other pathologies and disorders.

NOV3 nucleic acids and polypeptides are further useful in the generation of antibodies that bind immunospecifically to the novel substances of the invention for use in therapeutic or diagnostic methods. These antibodies may be generated according to methods known in the art, using prediction from hydrophobicity charts, as described in the "Anti-NOVX Antibodies" section below. The disclosed NOV3 protein has multiple hydrophilic regions, each of which

A disclosed NOV4 nucleic acid of 1500 nucleotides (also referred to as

SC140515441_A) encoding a novel Aurora-related kinase 1-like protein is shown in Table 4A. An open reading frame was identified beginning with a ATG initiation codon at nucleotides 182-184 and ending with a TAG codon at nucleotides 1391-1393. The start and stop codons are in bold letters, and the 5' and 3' untranslated regions are underlined.

TCATCTTAAATTTTTTAGCTGATATAGTTGTAATTTCTTAACTAGCTCATCTCTAGAGGATATGTA
ACATAAAACCTCAATTACTTGTGAATTATAGAGGTGTATCAGTTGGTTTAAAAGTGCTTTTATTGGGCT
GAGCTCTTGGAGACTCAGGCTCGCTTGGGTCAAGGCATCATGGACCAATCGAAGAAAATCGATTTTTCAGG
GCTGTTGAGGCTAAAATCCAGTTGGAGGTCAGAACATGTTTCTCGTACTCAGCAATTTCTTGTGAGA
ATCCATTACCTGCAAAATAGTGGCCAGGCTCAGTGGGTCTGTGTCTTCAAATTTCTCGCAGCTGTCTCT
TTGCAAGCAAAAAGCTTGTCTCAGTCAAGCCAGTTCAGAAATCAGAAGCAGAAGCAATTGCAGGCAAC
CAGTGTAACCTCATCTCGCTCGCCACAGGCACTGAATAACACCAAAACAGCAAGCATGCCCGCTGTCCGC
CTGAAAAATAATCTGTAGGAGGAATCGGCATCAAAACAGAAAAATGAAGAAATCAAAAAGAGCAATGGGCT
TTGGAAGACTTGAAATTTGGTCGCCCTCCGGGTAAAGGAAAGTTTGGTAAATGTTTATTGGCAAGAGAAAA
ACAAAGCAAGTTTATTCTGGCTCTTAGGTTGTTATTTTAAAGCTCAGCTGGAGAAAAGCAGGATGGAGCATC
AATCAGAAGAGAAAGTAGAAATACAGTCCCACCTCCAACATCTTAATAATACAGCTGTATGGTTATTTCT
CATGATGCCACCAGAGTCTACCTAATTTCTGGAATATACACCTTGAAACAGTCAATACAGAACTTCAGAA
ACTTTCAAAGTTTGATGACGAGACAATGCTCTATTATACAGAAATTGGCAAGTGCCCTGTCTTACTGTC
ATTCAAAACAGTTATTTATTCATAGAGAACTTAAGCCAGGACCACTTACTTCTTGATCAGCTGGAGAGCTTGA
ATTGCAAAATTTGGGTGGTCAGAACATGCTCCATCTTCCAGGAGACACTCTGTGGCAACCTGGCACTA
CCTGCCCCCGAAATGATTGAAGTCCGATGCATGATGAGAAGGTGGATCTCTGGAGCCTTGGAGTTCTTT
GCTGTGAATTTTATGTGGGAAGCTCCTTTTGAGGCAAAATACATCAAGAGACCTACAAAAGAAATATCA
CGGTTTGAGTTGACATTTCCCTGACTTTGTAAACAGGAGGCCAGGACCTATTTCAGACTGTGGAAGCA
TGTTCCAGCCAGAGGCCAATGCTCAGAGAAAGTATTTGAATACCCCTGGTACAGCAAAATTCATCAAAAC
CATCAATTTGCTCAAAACAAAGAATCAACTAGCAAGTATTTTAGGAATCGTGCAGGGGGAGAAATCCTTGA
GCCAGGCTGCTGTATAACCTCTCAGGAACATGCTACCAAAATTTATTTACCATTAGCTGCGCCTCAA
TCTAGAAC

The disclosed NOV4 nucleic acid sequence maps to chromosome 1 and has 1152 of 1212 bases (95%) identical to a gb:GENBANK-ID:AF008551|acc:AF008551 mRNA from *Homo sapiens* (*Homo sapiens* aurora-related kinase 1 (ARK1) mRNA, complete cds (E = 1.8e⁻²⁴³).

likely to be localized microbody (peroxisome) with a certainty of 0.3000, to the mitochondrial membrane space with a certainty of 0.1000, or to the lysosome(lumen) with a certainty of 0.1000.

Table 4B. Encoded NOV4 protein sequence (SEQ ID NO:14).

MDQSEENCISGPVEAKTPVGGPEHVLVTQQFPQCNPLPANSGQAQWVLCPSNSSORVPLQAQKLVSHPKV
QKQKQKQKLQATQSPVHPASRPLNNTQSNQKSLPAPENNPHEELKQAKNESKKRWQDALELIEIRPPGKG
KFNQVILAREKQSKFIFALRLVFKFAQLEKAGVEHQLRREVEITQSHLQHNPNIIRLQYFHDAIRVYLLEYT
PLETVNTEQLKQLSKFDEQRTATYITELASALSCHSKTATVIHRDIKPENLLGSAGELEIANFGWSEHAPSS
RRTTLCGTLDYLPPEMIEGRMHDEKVDLWSLGLVLCCEFLVNGKFPFEANTYQETKYRISRVEFTFPDFVTEG
ARDLISRLLKHVPSQRPMLEVLVEYPWITANSKSPNCNSKNESTSKYS

10 The disclosed NOV4 amino acid has 69 of 403 amino acid residues (91%) identical to, and 381 of 403 amino acid residues (94%) similar to, the 403 amino acid residue ptnr:SPTREMBL-ACC:O60445 protein from *Homo sapiens* (Human) (Aurora-Related Kinase 1 (E= 1.7e^{-198})).

15 Marrow, Brain, Cervix, Colon, Coronary Artery, Epidermis, Heart, Kidney, Liver, Lung,
Lymphoid tissue, Mammary gland/Breast, Ovary, Peripheral Blood, Placenta, Prostate, Testis,
Thalamus, Tonsils, Uterus. This information was derived by determining the tissue sources of
the sequences that were included in the invention.

20 pattern of (GENBANK-ID: gb:GENBANK-ID:AF008551|acc:AF008551) a closely related
aurora-related kinase 1 (ARK1) mRNA, complete cds homolog in species *Homo sapiens*.

NOV4 also has homology to the amino acid sequences shown in the BLASTP data listed in Table 4C.

Table 4C. BLAST results for NOV4

Gene Index/ Identifier	Protein/ Organism	Length (aa)	Identity (%)	Positives (%)	Expect
gi 12654873 gb AAH01280.1 AAH01280 (BC001280)	serine/threonine kinase 15 [Homo sapiens]	403	370/403 (91%)	381/403 (93%)	0.0

gi 13653970 ref XP_009546.3 (XM_009546)	serine/threonine kinase 15 [Homo sapiens]	403	369/403 (91%)	381/403 (93%)	0.0
gi 4507275 ref NP_03591.1 (NM_003600)	serine/threonine kinase 15; Serine/threonine protein kinase 15 [Homo sapiens]	403	369/403 (91%)	380/403 (93%)	0.0
gi 7446411 pir JC5974	aurora-related kinase 1 (EC 2.7.--.) - human	403	367/403 (91%)	379/403 (93%)	0.0
gi 4507279 ref NP_03149.1 (NM_003158)	serine/threonine kinase 6; Serine/threonine protein kinase-6; serine/threonine kinase 6 (aurora/IPL1-like) [Homo sapiens]	402	342/403 (84%)	360/403 (88%)	0.0

The homology of these sequences is shown graphically in the ClustalW analysis shown in Table 4D.

5

Table 4D. ClustalW Analysis of NOV4

- 1) NOV4 (SEQ ID NO:14)
- 2) gi|12654873|gb|AAH01280.1|AAH01280 (BC001280) serine/threonine kinase 15 [Homo sapiens] (SEQ ID NO:47)
- 3) gi|13653970|ref|XP_009546.3| (XM_009546) serine/threonine kinase 15 [Homo sapiens] (SEQ ID NO:48)
- 4) gi|4507275|ref|NP_003591.1| (NM_003600) serine/threonine kinase 15; Serine/threonine protein kinase 15 [Homo sapiens] (SEQ ID NO:49)
- 5) gi|7446411|pir||JC5974 aurora-related kinase 1 (EC 2.7.--.) - human (SEQ ID NO:50)
- 6) gi|4507279|ref|NP_003149.1| (NM_003158) serine/threonine kinase 6; Serine/threonine protein kinase-6; serine/threonine kinase 6 (aurora/IPL1-like) [Homo sapiens] (SEQ ID NO:51)

20

25

30

35

NOV410.....20.....30.....40.....50
gi 12654873	MDQSEENCISGPVVEAKTPVGGPEHVLVTQQFPQNPLPANSQQAQVVLCP
gi 13653970	MDRSKENCISGPVKATAPVGGPKRVLVTQQFPQNPLPVNSGQAQVVLCP
gi 4507275	MDRSKENCISGPVKATAPVGGPKRVLVTQQFPQNPLPVNSGQAQVVLCP
gi 7446411	MDRSKENCISGPVKATAPVGGPKRVLVTQQFPQNPLPVNSGQAQVVLCP
gi 4507279	MDRSKENCISGPVKATAPVGGPKRVLVTQQFPQNPLPVNSGQAQVVLCP
NOV460.....70.....80.....90.....100
gi 12654873	SNSSQRVPLQAQKLVSSHKPQVQKQKQLOATSVPHPSRPLNNTQKSKQ
gi 13653970	SNSSQRVPLQAQKLVSSHKPQVQKQKQLOATSVPHPSRPLNNTQKSKQ
gi 4507275	SNSSQRVPLQAQKLVSSHKPQVQKQKQLOATSVPHPSRPLNNTQKSKQ
gi 7446411	SNSSQRVPLQAQKLVSSHKPQVQKQKQLOATSVPHPSRPLNNTQKSKQ

gi|4507279| SNSSQRVPLQAQKLVSSHKPVQNKQKQLQATSVPHPVSRPLNNTQKSKQ

110 120 130 140 150

5 NOV4
gi|12654873| SPLSAPENNPEEELASKQKNEESKKRQWALEDLEIGRPLGKGFNGVYLA
gi|13653970| PLPSAPENNPEEELASKQKNEESKKRQWALEDLEIGRPLGKGFNGVYLA
gi|4507275| PLPSAPENNPEEELASKQKNEESKKRQWALEDLEIGRPLGKGFNGVYLA
gi|7446411| PLPSAPENNPEEELASKQKNEESKKRQWALEDLEIGRPLGKGFNGVYLA
10 gi|4507279| PLPSHLKILRRNWHQNRK-MKNCKEAVALEDFEIGRPLGKGFNGVYLA

160 170 180 190 200

15 NOV4
gi|12654873| REKQSKFILALRVLFKAQLEKAGVEHQLRREVEIQSHLHPNIRLYGYF
gi|13653970| REKQSKFILALKVLFKAQLEKAGVEHQLRREVEIQSHLRHPNIRLYGYF
gi|4507275| REKQSKFILALKVLFKAQLEKAGVEHQLRREVEIQSHLRHPNIRLYGYF
gi|7446411| REKQSKFILALKVLFKAQLEKAGVEHQLRREVEIQSHLRHPNIRLYGYF
20 gi|4507279| REKQSKFILALKVLFKAQLEKAGVEHQLRREVEIQSHLRHPNIRLYGYF

210 220 230 240 250

25 NOV4
gi|12654873| HDATRVYLILEYIPLGTVNTLQKLSKFDEQRTATYITELASALSCHSK
gi|13653970| HDATRVYLILEYAPLGTVYRELQKLSKFDEQRTATYITELANALSCHSK
gi|4507275| HDATRVYLILEYAPLGTVYRELQKLSKFDEQRTATYITELANALSCHSK
gi|7446411| HDATRVYLILEYAPLGTVYRELQKLSKFDEQRTATYITELANALSCHSK
30 gi|4507279| HDATRVYLILEYAPLGTVYRELQKLSKFDEQRTANLYNRITANALSCHSK

260 270 280 290 300

35 NOV4
gi|12654873| TVIHRDIKPENLLGSAGELKIADFGWSVHAPSSRRTTLCGTLDYLPPEM
gi|13653970| RVIHRDIKPENLLGSAGELKIADFGWSVHAPSSRRTTLCGTLDYLPPEM
gi|4507275| RVIHRDIKPENLLGSAGELKIADFGWSVHAPSSRRTTLCGTLDYLPPEM
gi|7446411| RVIHRDIKPENLLGSAGELKIADFGWSVHAPSSRRTTLCGTLDYLPPEM
40 gi|4507279| RVIHRDIKPENLLGSAGELKIADFGWSVHAPSSRRTTLCGTLDYLPPEM

310 320 330 340 350

45 NOV4
gi|12654873| IEGRMHDEKVDLWSLGVLCYEFVLGKPPFEANTYQETYKRISRVEFTFPD
gi|13653970| IEGRMHDEKVDLWSLGVLCYEFVLGKPPFEANTYQETYKRISRVEFTFPD
gi|4507275| IEGRMHDEKVDLWSLGVLCYEFVLGKPPFEANTYQETYKRISRVEFTFPD
gi|7446411| IEGRMHDEKVDLWSLGVLCYEFVLGKPPFEANTYQETYKRISRVEFTFPD
50 gi|4507279| IEGRMHDEKVDLWSLGVLCYEFVLGKPPFEANTYQETYKRISRVEFTFPD

360 370 380 390 400

55 NOV4
gi|12654873| FVTEGARDLISRLKHNPSQRPMLREVLEHPWITANSSKPSNCQNKESAS
gi|13653970| FVTEGARDLISRLKHNPSQRPMLREVLEHPWITANSSKPSNCQNKESAS
gi|4507275| FVTEGARDLISRLKHNPSQRPMLREVLEHPWITANSSKPSNCQNKESAS
gi|7446411| FVTEGARDLISRLKHNPSQRPMLREVLEHPWITANSSKPSNCQNKESAS
60 gi|4507279| FVTEGARDLISRLKHNPSQRPMLREVLEHPWITANSSKPSNCQNKESAS

65 NOV4
gi|12654873| KQS
gi|13653970| KQS
gi|4507275| KQS
gi|7446411| KQS
gi|4507279| KQS

Tables 4E-G lists the domain description from DOMAIN analysis results against NOV4. This indicates that the NOV4 sequence has properties similar to those of other proteins known to contain this domain.

gnl|Smart|smart00220, S_TKc, Serine/Threonine protein kinases, catalytic domain; Phosphotransferases. Serine or threonine-specific kinase subfamily. (SEQ ID NO:98)
CD-Length = 256 residues, 99.6% aligned
Score = 256 bits (653), Expect = 2e-69

5

NOV 3: 134 EIGRPPGKGKFGNVYLAREKQSKFILALRVLFKAQLEKAGVEHQLRREVEIQSHLQHPNI 193
 |+ ||| || |||||+|++ ++|++|+ | +|+ ++ ||++ | ||||
 Sbjct: 2 ELLEVLGKGAGFKVYLARDKKTGKLVAIKVIKKEKLK-KKRERILREIKILKKLDHPNI 60

10

NOV 3: 194 IRLYGYFHDA TRVYLILEYTPLETVNTELQKLSKFDEQRTATYITELASALSYCHSKTVI 253
 ++|| | | ++|++| | + | + | | ++ || | | + +|
 Sbjct: 61 VKLYDVFEDDDKLYLVMEYCEGDLFDLLKKRGRLSEDEARFYARQILSALEYLHSGQII 120

15

NOV 3: 254 HRDIKPENLLLSAGELEIANFGWS--EHAPSSRRTTLCGTLDYLPPEMIEGRMHDEKVD 311
 |||+|||+|| | | +++|+| + + + || | +|+ ||++ | + + + ||
 Sbjct: 121 HRDLKPENILLDSGDGHVKLADFLAKQLDSSGTLTTTFVGTPEYMAPEVLGLGKGYGKAVD 180

20

NOV 3: 312 LWSLGVLCCEFLVGKPPFEA-NTYQETYKRISRVEFTFPDF--VTEGARDLISRLLKHV 367
 +||||+ | | |||| + +|+ + || ++ |+|| +||
 Sbjct: 181 IWSLGVILYELLTGKPPFGDDQLALFKKIGKPPPPPPPEWKISPEAKDLIKLLLVKD 240

NOV 3: 368 PSQRPMLEVL EYPWI 383
 | +| | ||+|+
 Sbjct: 241 PEKRLTAEAELEHPFF 256

25

gnl|Pfam|pfam00069, kinase, Protein kinase domain (SEQ ID NO:99)
CD-Length = 256 residues, 100.0% aligned
Score = 221 bits (564), Expect = 5e-59

	NOV 3:	133	LEIGRPPGKGKGFNVYLAREKQSKFILALRVLFKAQLEKAGVEHQLRREVEIQSHLQHPN	192
			+ + + + +++ + + + +++	
30	Sbjct:	1	YELGEKLGSGAFGKVYKGKHKDTGEIVAIIKILKKRSLSE--KKKRFLEIQILRRLSHPN	58
	NOV 3:	193	IIRLYGYFHDATRVYLLILEYTPLETVNTEL-QKLSKFDEQRTATYITELASALSYCHSKT	251
			+ + + + + + + ++ +	
	Sbjct:	59	IVRLLGVFEEDDHLVLMVEYMEGGDLFDYLRNGLLLSEKEAKKIALQILRGLEYLHSRG	118
35	NOV 3:	252	VIHRDIKPENLLGSAGELEIANFGWS--EHAPSSRRTTLCGTLDYLPPEMIEGRMHDE	308
			++ + + + ++ + + + + + + ++ +	
	Sbjct:	119	IVHRDLKPENILLDENGTVKIADFGFLARKLESSSYEKLTTFVGTPPEYMAPEVLEGRGYSS	178
40	NOV 3:	309	KVDLWSLGLVLCCEFLVGKPPFEANTYQETYKRI---SRVEFTFPDFVTEGARDLISRLK	365
			+ + + + + + +	
	Sbjct:	179	KVDVWSLGVILYELLTGKLPFGIDPLEELFRIKERPRRLPLPNCSEELKDILKKCLN	238
	NOV 3:	366	HVPSQRPMLREVLEYPWI	383
			+ + + +	
45	Sbjct:	239	KDPEKRPTAKEILNHPWF	256

Table 4G Domain Analysis of NOV4

gnl|Smart|smart00219, TyrKc, Tyrosine kinase, catalytic domain;
Phosphotransferases. Tyrosine-specific kinase subfamily (SEQ ID
NO:100)
CD-Length = 258 residues, 99.6% aligned
Score = 127 bits (318), Expect = 2e-30

	NOV 3:	133	LEIGRPPGKGFNVLAREKQSKFILALRVLFKAQLEKAGVEHQ--LRREVEIQSHLQH	190
			+	
5	Sbjct:	1	LTLGKKLGEGAFGEVYKGTGKGGVE-VEVAVKTLKEDASEQQIEEFLREARLMRKLDH	59
	NOV 3:	191	PNIIRLYGYFHDATRVYLILEYTPLETVNTELQKLSK--FDEQRTATYITELASALSYCH	248
	Sbjct:	60	PNIVKLLGVCTEEELMIVMEYMEGGDLLDYLRKNRPKELSLDLLSFALQIARGMEYLE	119
10	NOV 3:	249	SKTVIHRDIKPENLLGSAGELEIANFGWSEHAPSSRRTTLCGTLD---YLPPEMIEGR	304
	Sbjct:	120	SKNFVHRDLAARNCLVGENKTVKIADFGLARDLYDDDYRKKKSPRLPIRWMAPESLKDG	179
15	NOV 3:	305	MHDEKVDLWSLGLVLCCE-FLVGKPPFEANTYQETYKRISRVEF-TFPDFVTEGARDLISR	362
			+	
	Sbjct:	180	KFTSKSDVWSFGVLLWEIFTLGESYPGMSNEEVLEYLKKGYRLPQPPNCPDEIYDMLQ	239
	NOV 3:	363	LLKHVPSQRPMREVLEY	380
20	Sbjct:	240	CWAEDPEDRPTFSEVER	257

Amplification of chromosome 20q DNA has been reported in a variety of cancers. DNA amplification on 20q13 has also been correlated with poor prognosis among axillary node-negative breast tumor cases. Sen et al. (1997) cloned a partial cDNA encoding STK15 (also known as BTAK and aurora2) from this amplicon and found that it is amplified and overexpressed in 3 human breast cancer cell lines. STK15 encodes a centrosome-associated kinase. Zhou et al. (1998) found that STK15 is involved in the induction of centrosome duplication-distribution abnormalities and aneuploidy in mammalian cells. Centrosomes appear to maintain genomic stability through the establishment of bipolar spindles during cell division, ensuring equal segregation of replicated chromosomes to 2 daughter cells. Deregulated duplication and distribution of centrosomes are implicated in chromosome segregation abnormalities, leading to aneuploidy seen in many cancer cell types. Zhou et al. (1998) found amplification of STK15 in approximately 12% of primary breast tumors, as well as in breast, ovarian, colon, prostate, neuroblastoma, and cervical cancer cell lines. Additionally, high expression of STK15 mRNA was detected in tumor cell lines without evidence of gene amplification. Ectopic expression of STK15 in mouse NIH 3T3 cells led to the appearance of abnormal centrosome number (amplification) and transformation in vitro. Finally, overexpression of STK15 in near-diploid human breast epithelial cells revealed similar centrosome abnormality, as well as induction of aneuploidy. These findings suggested that STK15 is a critical kinase-encoding gene, whose overexpression leads to centrosome

amplification, chromosomal instability, and transformation in mammalian cells. Zhou et al. (1998) found that the open reading frame of the full-length STK15 cDNA sequence encodes a 403-amino acid protein with a molecular mass of approximately 46 kD. STK6 (602687), also referred to as AIK, is highly homologous to STK15. The *Drosophila* 'aurora' and *S. cerevisiae* Ipl1 STKs are involved in mitotic events such as centrosome separation and chromosome segregation. Using a degenerate primer-based PCR method to screen for novel STKs, Shindo et al. (1998) isolated mouse and human cDNAs encoding STK15, which they termed ARK1 (aurora-related kinase-1). Cell cycle and Northern blot analyses showed that peak expression of STK15 occurs during the G2/M phase and then decreases. By interspecific backcross mapping, Shindo et al. (1998) mapped the mouse *Stk15* gene to the distal region of chromosome 2 in a region showing homology of synteny with human 20q

The disclosed NOV4 nucleic acid of the invention encoding a Aurora-related kinase 1-like protein includes the nucleic acid whose sequence is provided in Table 4A or a fragment thereof. The invention also includes a mutant or variant nucleic acid any of whose bases may be changed from the corresponding base shown in Table 4A while still encoding a protein that maintains its Aurora-related kinase 1-like activities and physiological functions, or a fragment of such a nucleic acid. The invention further includes nucleic acids whose sequences are complementary to those just described, including nucleic acid fragments that are complementary to any of the nucleic acids just described. The invention additionally includes nucleic acids or nucleic acid fragments, or complements thereto, whose structures include chemical modifications. Such modifications include, by way of nonlimiting example, modified bases, and nucleic acids whose sugar phosphate backbones are modified or derivatized. These modifications are carried out at least in part to enhance the chemical stability of the modified nucleic acid, such that they may be used, for example, as antisense binding nucleic acids in therapeutic applications in a subject. In the mutant or variant nucleic acids, and their complements, up to about 5 percent of the bases may be so changed.

The disclosed NOV4 protein of the invention includes the Aurora-related kinase 1-like protein whose sequence is provided in Table 4B. The invention also includes a mutant or variant protein any of whose residues may be changed from the corresponding residue shown in Table 4B while still encoding a protein that maintains its Aurora-related kinase 1-like activities and physiological functions, or a functional fragment thereof. In the mutant or variant protein, up to about 9 percent of the residues may be so changed.

The protein similarity information, expression pattern, and map location for the Aurora-related kinase 1-like protein and nucleic acid (NOV4) disclosed herein suggest that

NOV4 may have important structural and/or physiological functions characteristic of the citron kinase-like family. Therefore, the NOV4 nucleic acids and proteins of the invention are useful in potential diagnostic and therapeutic applications. These include serving as a specific or selective nucleic acid or protein diagnostic and/or prognostic marker, wherein the presence or amount of the nucleic acid or the protein are to be assessed, as well as potential therapeutic applications such as the following: (i) a protein therapeutic, (ii) a small molecule drug target, (iii) an antibody target (therapeutic, diagnostic, drug targeting/cytotoxic antibody), (iv) a nucleic acid useful in gene therapy (gene delivery/gene ablation), and (v) a composition promoting tissue regeneration in vitro and in vivo.

The NOV4 nucleic acids and proteins of the invention are useful in potential diagnostic and therapeutic applications implicated in various diseases and disorders described below. For example, the compositions of the present invention will have efficacy for treatment of patients suffering from breast, ovarian, colon, prostate, neuroblastoma, and cervical cancer, Cardiomyopathy, Atherosclerosis, Hypertension, Congenital heart defects, Aortic stenosis, Atrial septal defect (ASD), Atrioventricular (A-V) canal defect, Ductus arteriosus, Pulmonary stenosis, Subaortic stenosis, Ventricular septal defect (VSD), valve diseases, Tuberosclerosis, Scleroderma, Obesity, Transplantation, Diabetes, Von Hippel-Lindau (VHL) syndrome, Pancreatitis, Alzheimer's disease, Stroke, hypercalcaemia, Parkinson's disease, Huntington's disease, Cerebral palsy, Epilepsy, Lesch-Nyhan syndrome, Multiple sclerosis, Ataxia-telangiectasia, Leukodystrophies, Behavioral disorders, Addiction, Anxiety, Pain, and Neuroprotection and/or other pathologies. The NOV4 nucleic acid, or fragments thereof, may further be useful in diagnostic applications, wherein the presence or amount of the nucleic acid or the protein are to be assessed.

NOV4 nucleic acids and polypeptides are further useful in the generation of antibodies that bind immunospecifically to the novel substances of the invention for use in therapeutic or diagnostic methods. These antibodies may be generated according to methods known in the art, using prediction from hydrophobicity charts, as described in the "Anti-NOVX Antibodies" section below. For example the disclosed NOV4 protein have multiple hydrophilic regions, each of which can be used as an immunogen. In one embodiment, contemplated NOV4 epitope is from about amino acids 1 to 10. In another embodiment, a NOV4 epitope is from about amino acids 15 to 160. In additional embodiments, NOV4 epitopes are from about amino acids 175 to 210, from about amino acids 220 to 240, from about amino acids 250 to 270, from about amino acids 280 to 320, from about amino acids 340 to 375, and from about amino acids 380 to 400. This novel protein also has value in development of powerful assay

system for functional analysis of various human disorders, which will help in understanding of pathology of the disease and development of new drug targets for various disorders.

NOV5

A disclosed NOV5 nucleic acid of 1500 nucleotides (designated CuraGen Acc. No. SC44326718_A) encoding a novel 26S protease regulatory subunit 4-like protein is shown in Table 5A. An open reading frame was identified beginning with an ATG initiation codon at nucleotides 101-103 and ending with a TAG codon at nucleotides 1427-1429. A putative untranslated region downstream from the termination codon is underlined in Table 5A, and the start and stop codons are in bold letters.

10

Table 5A. NOV5 Nucleotide Sequence (SEQ ID NO:15)
<p> GTATCCCCAAGAGAAAAATACGCATCAAAAATTAGGAACTTAGAAATGATAGTTGAGGTGGAGGAACTTCC AGCAGTGGCAGCTCAAGTGGCCAAGACAAGATGGGTCAAAGTCAGGGTGATGGTCATGGTCCTAGACGTG GCAAGAAGGATGAAAAGGACAAGAAAAATAAGTACGAACCTCTTGTACCAACTAGAGTGGCGGAAAAAGA AGAAAAACAAAGGACAAGATGTTGCCAGTAACTGCCACTGGTGACACTTCACACTCAGTGTGCGTTA AAATTACTGAAGTTAGAGAGAATAAAGACTACCTTCTCATGGTGGAAGAATTCATTAGAAATCAGGAAC AAATAAACTATTAGAAGAAAAGCAAGAGGAGGGAAGATCAAAAAGTGGATGATCTGAGGGGGACCCCAAT GTCAGTAGGAACTTGAAGAGATCATCGATGACAATCATGCCATTGTGTCTACATCTGTGGGCTCAGAA CACTATGACAGCATTATTTCATTGTAGAGAAGGATCTGCTGGAACCTGGCTGCTCGATCTGCTCAGAC ACAAGGTACATGCGGTGATAGGGGTGCTGATGGATGATACGGGTCCCTGGTCACAATGATGAAGGTGGA GAAGCCCCCAGGAGACCTATGTCAATCTGCGGGGTGGACAACCAAATTCAGGAAATTAAGGAATCT ATGGAGCTTCCTCTCCCCATCTGAATATTATGAAGAGATGGGTACAAAGCCTCTAAAGGGGTCATTT TCTGTGGTCCACCTGGCACAGGTAAACCTTGTAGCCAAAGCAGTAGCAAAACCAACCTCAGCCACTTT CTTGAGAGTGGTTGGCTCTGAACTTATTCAAGAGTACCTAGGTGATGGGCCCAAACCTCGTACGGCAAGTA TTTCAAGTTGCTGAAGAACATGCACCATCCATCATGTTTACTGATGAAATGAAGCCATTGGGACAAAAA GATATGACTCCAATTCTGGTGGTGAGAGAGAAATTCAGCAAAACAATGTTGGAATGGAACTGTTGAACCA ATTGGGTGGATTGATTCTAGGGAAGATGTGAAAGTTATCATGGCCACAAAACAAGTAGAACTTTGGAT CCAGTACTTATCAGACCAGGCCGATTGACAAGAAGATCGAGTTCCACCTGCCTGATGAAAAGACTAAGA AGCATCTTTTCAAGATTCACACAAGCAGGATGACACTGGCCAAATGATGTAACCTGGACGACTTGATCAT GGCTAAAGATGACTTCTCTGGTCTGACATCAAGGCAATCTGTACAGAGCTGGTCTGATGGCCTTAAGA GACATAGAATGAAAGCAACAAATGAAGACTTCAAAAATCTATAGAAAGTGTCTTTATAAGAAACACG AAGGCATCCCTGAGGGGCTTTATCTCTAGTGAACCCGCTGCCATCAGGAAGATGGTTGGGAGATTTC CAACCCCTGAAAGGGATGAGGTGGGGGAG </p>

The nucleic acid sequence NOV5, located on chromosome 5 has 1347 of 1447 bases (93%) identical to a gb:GENBANK-ID:HUM26SPSIV|acc:L02426 mRNA from *Homo sapiens* (Human 26S protease (S4) regulatory subunit mRNA, complete cds (E = 2.4e⁻²⁷⁷).

A NOV5 polypeptide (SEQ ID NO:16) encoded by SEQ ID NO:15 is 442 amino acid residues and is presented using the one letter code in Table 5B. Signal P, Psort and/or Hydropathy results predict that NOV5 has no signal peptide and is likely to be localized in the cytoplasm with a certainty of 0.4500. In other embodiments, NOV5 may also be localized to the microbody (peroxisome) with a certainty of 0.3000, the mitochondrial matrix space with a certainty of 0.1000, or the lysosome (lumen) with a certainty of 0.1000.

Table 5B. NOV5 protein sequence (SEQ ID NO:16)

MGQSQGDGHGPRRGKKDEKDKKNKYEPLVPTRVAEKEEKTGQDVASKLPLVTLHTQCRLKLLKLERIKDYLLM
VEEFIRNQEQIKLLEEKQEEGRSKVDDLRTGTPMSVGNLEEIIDNHAIVSTSVGSEHYDSIISFVEKDILLEPGC
SILLRHKVHAVIGVLMDDTGPLVTMMKVEKAPQETTYNTGGLDNQIQEIKESMELPLPHPEYYEEMGTKPPKGV
ILCGPPGTGKTLAKAVANQTSATFLRVVGSELIQKYLGDGPKLVRQVFQVAEEHAPSIMFTDEIEAIGTKRYD
SNSGGEREIQQTMLELELLNQLGGFDSREDVKVIMATKQVETLDPVLIRPGRIDKKIEFHLPEDEKTKKHIFQIH
TSRMTLANDVTLLDLIMAKDDFSGADIKAICTEAGLMALREHRMKATNEDFKKSIESVLYKKHEGIEPEGLYL

The full amino acid sequence of the protein of the invention was found to have 383 of 442 amino acid residues (86%) identical to, and 405 of 442 amino acid residues (91%) similar to, the 440 amino acid residue ptrn:SWISSPROT-ACC:P49014 protein from *Mus musculus* (Mouse), and *Rattus norvegicus* (Rat) (26S Protease Regulatory Subunit 4 (P26S4) (E = 1.7e⁻²⁰⁰).

NOV5 also has homology to the amino acid sequences shown in the BLASTP data listed in Table 5C.

Table 5C. BLAST results for NOV5

Gene Index/ Identifier	Protein/ Organism	Length (aa)	Identity (%)	Positives (%)	Expect
gi 4506207 ref NP_02793.1 (NM_002802)	proteasome (prosome, macropain) 26S subunit, ATPase, 1; Proteasome 26S subunit, ATPase, 1 [Homo sapiens]	440	382/442 (86%)	405/442 (91%)	0.0
gi 6679501 ref NP_032973.1 (NM_008947)	protease (prosome, macropain) 26S subunit, ATPase 1 [Mus musculus]	440	383/442 (86%)	405/442 (90%)	0.0
gi 345717 pir A44468	26S proteasome regulatory chain 4 [validated] - human	440	381/442 (86%)	404/442 (91%)	0.0
gi 16741033 gb AAH16368.1 AAH16368 (BC016368)	protease (prosome, macropain) 26S subunit, ATPase 1 [Homo sapiens]	440	382/442 (86%)	404/442 (90%)	0.0
gi 2492516 sp Q90732 PRS4_CHICK	26S PROTEASE REGULATORY SUBUNIT 4 (P26S4)	440	378/442 (85%)	402/442 (90%)	0.0

The homology of these sequences is shown graphically in the ClustalW analysis shown in Table 5D.

Table 5D ClustalW Analysis of NOV5

- 1) NOV5 (SEQ ID NO:16)
- 2) gi|4506207|ref|NP_02793.1| (NM_002802) proteasome (prosome, macropain) 26S subunit, ATPase, 1; Proteasome 26S subunit, ATPase, 1 [Homo sapiens] (SEQ ID NO:52)
- 3) gi|6679501|ref|NP_032973.1| (NM_008947) protease (prosome, macropain) 26S subunit, ATPase 1 [Mus musculus] (SEQ ID NO:53)
- 4) gi|345717|pir|A44468 26S proteasome regulatory chain 4 [validated] - human (SEQ ID NO:54)

5) gi|16741033|gb|AAH16368.1|AAH16368 (BC016368) protease (prosome, macropain) 26S subunit, ATPase 1 [Homo sapiens] (SEQ ID NO:55)
6) gi|2492516|sp|Q90732|PRS4_CHICK 26S PROTEASE REGULATORY SUBUNIT 4 (P26S4) (SEQ ID NO:56)

5

10

		10	20	30	40	50
NOV5		MGQSQSGDGHGPRRGKKDE	KKKKKYEP	PLVPTRVAK	KEEKTGQDV	ASKLP
gi 4506207		MGQSQSGGHGPGGGKKDD	EDKKKKYEP	PPVTRVGKKKKKT	KGPDAA	SKLP
gi 6679501		MGQSQSGGHGPGGGKKDD	DKKKKKYEP	PPVTRVGKKKKKT	KGPDAA	SKLP
gi 345717		MGQSQSGGHGPGGGKKDD	EDKKKKYEP	PPVTRVGKKKKKT	KGPDAA	SKLP
gi 16741033		MGQSQSGGHGPGGGKKDD	DKKKKKYEP	PPVTRVGKKKKKT	KGPDAA	SKLP
gi 2492516		MGQSQSGGHGPGGGKKDD	DKKKKKYEP	PPVTRVGKKKKKT	KGPDAA	SKLP

15 60 70 80 90 100

NOV5 LVT¹LHTQ²CRLK³LKL⁴LERIK⁵DYLL⁶MEEF⁷IRN⁸QEQ⁹IK¹⁰LLEEK¹¹QEE¹²CR¹³SK¹⁴VD¹⁵

gi|4506207| LVT¹PHTQ²CRLK³LKL⁴LERIK⁵DYLL⁶MEEF⁷IRN⁸QEQ⁹MK¹⁰PLEEK¹¹QEE¹²ERS¹³SK¹⁴VD¹⁵

gi|6679501| LVT¹PHTQ²CRLK³LKL⁴LERIK⁵DYLL⁶MEEF⁷IRN⁸QEQ⁹MK¹⁰PLEEK¹¹QEE¹²ERS¹³SK¹⁴VD¹⁵

20 gi|345717| LVT¹PHTQ²CRLK³LKL⁴LERIK⁵DYLL⁶MEEF⁷IRN⁸QEQ⁹MK¹⁰PLEEK¹¹QEE¹²ERS¹³SK¹⁴VD¹⁵

gi|16741033| LVT¹PHTQ²CRLK³LKL⁴LERIK⁵DYLL⁶MEEF⁷IRN⁸QEQ⁹MK¹⁰PLEEK¹¹QEE¹²ERS¹³SK¹⁴VD¹⁵

gi|2492516| LVT¹PHTQ²CRLK³LKL⁴LERIK⁵DYLL⁶MEEF⁷IRN⁸QEQ⁹MK¹⁰PLEEK¹¹QEE¹²ERS¹³SK¹⁴VD¹⁵

25 NOV5 DLRGTPMSVGNLEEIIDDNHAIVSTSVGSEHYVDSIIISFVEKDLLEPGCSV
gi|4506207| DLRGTPMSVGTLEEIIDNHAIVSTSVGSEHYVSILSFVDKDLLEPGCSV
gi|6679501| DLRGTPMSVGTLEEIIDNHAIVSTSVGSEHYVSILSFVDKDLLEPGCSV
gi|345717| DLRGTPMSVGTLEEIIDNHAIVSTSVGSEHYVSILSFVDKDLLEPGCSV
30 gi|16741033| DLRGTPMSVGTLEEIIDNHAIVSTSVGSEHYVSILSFVDKDLLEPGCSV
gi|2492516| DLRGTPMSVGTLEEIIDNHAIVSTSVGSEHYVSILSFVDKDLLEPGCSV

35 NOV5
gi|4506207|
gi|6679501|
gi|345717|
gi|16741033|
40 gi|2492516|

160 170 180 190 200

LLRHKKVHAVIGVLMDDTDPLVTVMKVEKAPQETYNATGGLDNQIQEIKES
LLNHKKVHAVIGVLMDDTDPLVTVMKVEKAPQETYADIGGLDNQIQEIKES
LLNHKKVHAVIGVLMDDTDPLVTVMKVEKAPQETYADIGGLDNQIQEIKES
LLNHKKVHAVIGVLMDDTDPLVTVMKVEKAPQETYADIGGLDNQIQEIKES
LLNHKKVHAVIGVLMDDTDPLVTVMKVEKAPQETYADIGGLDNQIQEIKES
LLNHKKVHAVIGVLMDDTDPLVTVMKVEKAPQETYADIGGLDNQIQEIKES

45

		210	220	230	240	250
NOVS		MELPLPHPEYYEEMG	IKPPKGVIL	GPPPGTGKTL	LAKAVANQTS	SATFLRV
gi 4506207		VELPLTHPEYYEEMG	IKPPKGVILY	GPPPGTGKTL	LAKAVANQTS	SATFLRV
gi 6679501		VELPLTHPEYYEEMG	IKPPKGVILY	GPPPGTGKTL	LAKAVANQTS	SATFLRV
gi 345717		VELPLTHPEYYEEMG	IKPPKGVILY	GPPPGTGKTL	LAKAVANQTS	SATFLRV
gi 16741033		VELPLTHPEYYEEMG	IKPPKGVILY	GPPPGTGKTL	LAKAVANQTS	SATFLRV
gi 2492516		VELPLTHPEYYEEMG	IKPPKGVILY	GPPPGTGKTL	LAKAVANQTS	SATFLRV

260 270 280 290 300

NOV5 VGSELIQKYLGDGPKLVRELFRVAEEHAPSIVFIDEIDAIGTKRYDSNSG

gi | 4506207 | VGSELIQKYLGDGPKLVRELFRVAEEHAPSIVFIDEIDAIGTKRYDSNSG

55 gi | 6679501 | VGSELIQKYLGDGPKLVRELFRVAEEHAPSIVFIDEIDAIGTKRYDSNSG

gi | 345717 | VGSELIQKYLGDGPKLVRELFRVAEEHAPSIVFIDEIDAIGTKRYDSNSG

gi | 16741033 | VGSELIQKYLGDGPKLVRELFRVAEEHAPSIVFIDEIDAIGTKRYDSNSG

gi | 2492516 | VGSELIQKYLGDGPKLVRELFRVAEEHAPSIVFIDEIDAIGTKRYDSNSG

60

310 320 330 340 350

NOV5 GEREIQITMLELLLNQLDGFDSRGDVKVI³¹⁰MATKQVETLDPVILIRPGRID

gi|4506207| GEREIQRTM--LELLNQLDGFDSRGDVKVI³²⁰MATNRIETLDPALIRPGRID

gi|6679501| GEREIQRTM--LELLNQLDGFDSRGDVKVI³³⁰MATNRIETLDPALIRPGRID

65

gi|345717| GEREIQRTM--LELLNQLDGFDSRGDVKVI³⁴⁰MATNRIETLDPALIRPGRID

gi|16741033| GEREIQRTM--LELLNQLDGFDSRGDVKVI³⁵⁰MATNRIETLDPALIRPGRID

qi|2492516| GEREIQRTM--LELLNQLDGFDSRGDVKVI³¹⁰MATNRIETLDPALIRPGRID

70 360 370 380 390 400

.....|.....|.....|.....|.....|.....|.....|.....|.....|.....|.....|

NOV 4: 259 YLGDGPKLVQRVFQVAEEHAPSIMFTDEIEAIGTKRYDSNSGGEREIQQTMLELELLNQL 318
 | | + + | + | + + | | + + + + | | | |
 Sbjct: 61 LSGSGGQRIRLALALARKLKPDLVILDEITSLLDAAEQE-----ALLLLEELLRL 111

5 NOV 4: 319 GGFDSDREDVKVIMATKQVETLDPVLIRPGRIDKKIEFHLPD 359
 | + | | | | | | + | | + + |
 Sbjct: 112 LLLLKEENVTVIATTNDETDLIPALLRR-RFDRRIVLLRIL 151

Ubiquitinated proteins are degraded by a 26S ATP-dependent protease. The protease is composed of a 20S catalytic proteasome and 2 PA700 regulatory modules. The PA700 complex is composed of multiple subunits, including at least 6 related ATPases and approximately 15 non-ATPase polypeptides. Tanahashi et al. (1998) stated that each of the 6 ATPases, namely PSMC1, PSMC2 (154365), PSMC3 (186852), PSMC4 (602707), PSMC5 (601681), and PSMC6 (602708), contains an AAA (ATPases associated with diverse cellular activities) domain (see PSMC5). Dubiel et al. (1992) cloned cDNAs encoding subunit 4 (S4) of the 26S protease by screening a HeLa cell cDNA library with probes that were produced using the protein sequence. The 440-amino acid protein has a molecular mass of 51 kD by SDS-PAGE. By fluorescence in situ hybridization, Tanahashi et al. (1998) mapped the human PSMC1 gene to 19p13.3. Hoyle and Fisher (1996) found that the human and mouse PSMC1 proteins have 99% amino acid identity. They reported that the mouse Psmc1 gene contains at least 11 exons. By analysis of an interspecific backcross, Hoyle and Fisher (1996) mapped the mouse Psmc1 gene to chromosome 12. Nomenclature note: The PSMC1 gene product, which Dubiel et al. (1992) called subunit 4 (S4), is distinct from the PSMC4 (602707) gene product.

The disclosed NOV5 nucleic acid of the invention encoding a 26S protease regulatory subunit 4 -like protein includes the nucleic acid whose sequence is provided in Table 5A or a fragment thereof. The invention also includes a mutant or variant nucleic acid any of whose bases may be changed from the corresponding base shown in Table 5A while still encoding a protein that maintains its 26S protease regulatory subunit 4 -like activities and physiological functions, or a fragment of such a nucleic acid. The invention further includes nucleic acids whose sequences are complementary to those just described, including nucleic acid fragments that are complementary to any of the nucleic acids just described. The invention additionally includes nucleic acids or nucleic acid fragments, or complements thereto, whose structures include chemical modifications. Such modifications include, by way of nonlimiting example, modified bases, and nucleic acids whose sugar phosphate backbones are modified or derivatized. These modifications are carried out at least in part to enhance the chemical stability of the modified nucleic acid, such that they may be used, for example, as antisense binding nucleic acids in therapeutic applications in a subject. In the mutant or variant nucleic acids, and their complements, up to about 7 percent of the bases may be so changed.

The disclosed NOV5 protein of the invention includes the 26S protease regulatory subunit 4 -like protein whose sequence is provided in Table 5B. The invention also includes a mutant or variant protein any of whose residues may be changed from the corresponding residue shown in Table 5B while still encoding a protein that maintains its 26S protease regulatory subunit 4 -like activities and physiological functions, or a functional fragment thereof. In the mutant or variant protein, up to about 14 percent of the residues may be so changed.

The protein similarity information, expression pattern, and map location for the 26S protease regulatory subunit 4-like protein and nucleic acid (NOV5) disclosed herein suggest that this NOV5 protein may have important structural and/or physiological functions characteristic of the 26S protease regulatory subunit 4 family. Therefore, the NOV5 nucleic acids and proteins of the invention are useful in potential diagnostic and therapeutic applications. These include serving as a specific or selective nucleic acid or protein diagnostic and/or prognostic marker, wherein the presence or amount of the nucleic acid or the protein are to be assessed, as well as potential therapeutic applications such as the following: (i) a protein therapeutic, (ii) a small molecule drug target, (iii) an antibody target (therapeutic, diagnostic, drug targeting/cytotoxic antibody), (iv) a nucleic acid useful in gene therapy (gene delivery/gene ablation), and (v) a composition promoting tissue regeneration in vitro and in vivo.

The NOV5 nucleic acids and proteins of the invention are useful in potential diagnostic and therapeutic applications implicated in various diseases and disorders described below. For example, the compositions of the present invention will have efficacy for treatment of patients suffering from cataract and Aphakia, Alzheimer's disease, neurodegenerative disorders, inflammation and modulation of the immune response, viral pathogenesis, aging-related disorders, neurologic disorders, cancer and/or other pathologies. The NOV5 nucleic acids, or fragments thereof, may further be useful in diagnostic applications, wherein the presence or amount of the nucleic acid or the protein are to be assessed.

NOV5 nucleic acids and polypeptides are further useful in the generation of antibodies that bind immunospecifically to the novel substances of the invention for use in therapeutic or diagnostic methods. These antibodies may be generated according to methods known in the art, using prediction from hydrophobicity charts, as described in the "Anti-NOVX Antibodies" section below. For example, the disclosed NOV5 protein has multiple hydrophilic regions, each of which can be used as an immunogen. In one embodiment, a contemplated NOV5 epitope is from about amino acids 5 to 50. In another embodiment, a NOV5 epitope is from

about amino acids 75 to 125. In additional embodiments, NOV5 epitopes are from about amino acids 175 to 225, from about amino acids 280 to 320, from about amino acids 330 to 380, and from about amino acids 390 to 440. These novel proteins can be used in assay systems for functional analysis of various human disorders, which will help in understanding of pathology of the disease and development of new drug targets for various disorders.

NOV6

A disclosed NOV6 nucleic acid of 1020 nucleotides (also referred to as GMAC073364_A_da1) encoding a novel MITSUGUMIN29-like protein is shown in Table 6A. An open reading frame was identified beginning with an ATG initiation codon at nucleotides 2-4 and ending with a TAA codon at nucleotides 818-820. Putative untranslated regions upstream from the initiation codon and downstream from the termination codon are underlined in Table 6A, and the start and stop codons are in bold letters.

Table 6A. NOV6 Nucleotide Sequence (SEQ ID NO:17)
<p><u>CATGTCCTCGACCGAGAGCGCCGCCGACGCGGACAAAGTCGCCGCCAGCAGGTGGACC</u> GCCTACTCGTGGGGCTGCGCTGGCGGCGGCTGGAGGAGCCGCTGGGCTTCATCAAAGTTCTC CAGTGGCTCTTTGCTATTTTCGCCTTCGGGTCCTGTGGCTCCTACAGCGGGAGACAGGAGC AATGGTTTCGCTGCAACAACGAAGCCAAGGACGTGAGCTCCATCATCGTTGCATTGGCTATC CCTTCAGGTTGCACCGGATCCAATATGAGATGCCCTCTGCGATGAAGAGTCCAGCTCCAAG ACCATGCACCTCATGGGGGACTTCTCTGCACCCGCCGAGTTCCTCGTGACCCTTGGCATCTT TTCCTTCTTCTATACCATGGCTGCCCTAGTTATCTACCTGCGCTTCCACAACCTCTACACAG AGAACAACGCTTCCCGCTGGTGGACTTCTGTGTGACTGTCTCCTTCACCTTCTTCTGGCTG GTAGCTGCAGCTGCCTGGGGCAAGGGCCTGACCGATGTCAAGGGGGCCACACGACCATCCAG CTTGACAGCAGCCATGTCAGTGTGCCATGGAGAGGAAGCAGTGTGAGTGCAGTGCCTGGGGCCACGC CCTCTATGGGCTGGCCAACATCTCCGTGCTCTTTGGCTTTATCAACTTCTTCTGTGGGCC GGGAACGTGGTTTGTGTTCAAGGAGACCCCGTGGCATGGACAGGGCCAGGGCCAGGACCA GGACCAGGACAGGACAGGGCCAGGGTCCAGCCAGGAGAGTGCAGCTGAGCAGGGAGCAG TGGAGAAGCAGTAAGCAGCCCCCACCT</p>

The NOV6 nucleic acid was identified on chromosome 3 and has 727 of 805 bases (90%) identical to a gb:GENBANK-ID:AB004816|acc:AB004816.1 mRNA from *Oryctolagus cuniculus* (*Oryctolagus cuniculus* mRNA for mitsugumin29, complete cds (E = 2.5e⁻¹⁴²).

A disclosed NOV6 polypeptide (SEQ ID NO:18) encoded by SEQ ID NO:17 is 272 amino acid residues and is presented using the one-letter code in Table 6B. Signal P, Psort and/or Hydropathy results predict that NOV6 has a signal peptide and is likely to be localized on the plasma membrane with a certainty of 0.6000. In other embodiments, NOV6 may also be localized to the Golgi body with a certainty of 0.4000, the endoplasmic reticulum (membrane) with a certainty of 0.3000, or the nucleus with a certainty of 0.1000. The most likely cleavage site for NOV6 is between positions 57 and 58, SYS-GE.

[illegible]

The homology of these sequences is shown graphically in the ClustalW analysis shown in Table 6D.

Table 6D Clustal W Sequence Alignment

5	1) NOV6 (SEQ ID NO:18)
	2) gi 3077703 dbj BAA25784.1 (AB004816) mitsugumin29 [Oryctolagus cuniculus] (SEQ ID NO:57)
	3) gi 6678874 ref NP_032622.1 (NM_008596) mitsugumin 29 [Mus musculus] (SEQ ID NO:58)
10	4) gi 12836843 dbj BAB23831.1 (AK005132) putative [Mus musculus] (SEQ ID NO:59)
	5) gi 1351168 sp P20488 SYPH_BOVIN SYNAPTOPHYSIN (MAJOR SYNAPTIC VESICLE PROTEIN P38) (SEQ ID NO:60)
	6) gi 2134413 pir I50720 synaptophysin IIa - chicken (SEQ ID NO:61)
15	
	10 20 30 40 50
	NOV6 MSSTESAGRTADKSPRQVDRLLVGLRWRRLEPLGFIKVLQWLFAIFAF
	gi 3077703 MSSTESPSRAADKSPRQVDRLLVGLRWRRLEPLGFIKVLQWLFAIFAF
	gi 6678874 MSSTESPGRTSDKSPRQVDRLLVGLRWRRLEPLGFIKVLQWLFAIFAF
20	gi 12836843 -----MDPVSOVASAGTFRALKEPLAFLRALELLFAMFAF
	gi 1351168 -----MDVVNQLVAGGQFRVVKLEPLGFVKVLQWVFAIFAF
	gi 2134413 -----MCMVLFAPLFAIFAF
25	60 70 80 90 100
	NOV6 GSCGSYSGETGAMVRCNNEAKDVSSIIVAFGYPPFRLHRTQYEMPLQDEES
	gi 3077703 GSCGSYSGETGAMVRCNNEAKDVSSIIVLFCYPPFRLHRTQYEMPLQDDDS
	gi 6678874 GSCGSYSGETGALVLCNNEAKDVSSIIVLFCYPPFRLYQYQYEMPLQDDDS
	gi 12836843 ATCGGYSGLRLSVDVCKNTESNLSIDIAFAYPFRLOQVTFEVPICEGK-
30	gi 1351168 ATCGSYSGEQLQLSVDCAKNTKSDLNIEVEFEYPPFRLHVEYFEAPTQCG--
	gi 2134413 ATCGGYSGLRLSVDCAKNTKSDLNIDIAFAYPFRLHQVNFDAPTCEGK-
35	110 120 130 140 150
	NOV6 SSKTMHLMGDFSAPAEFFVTLCIFSFFFYTMAALVIYTRFHNLVTENKRFP
	gi 3077703 SSKTMHLMGDFSAPAEFFVTLCIFSFFFYTMAALVVIYTRFHKLVTENKRFP
	gi 6678874 TSKTMHLMGDFSAPAEFFVTLCIFSFFFYTMAALVVIYTRFHKLVTENKRFP
	gi 12836843 EQCKIALVGDSSSAEFFVTVAFAFLYSLAATVVVYDFONKYRENNRGP
	gi 1351168 DPKKIFLVGNYSSEAEFFVTVAFAFLYSLAATVVVYDFONKYRENNKGP
40	gi 2134413 RRETSLIGDFSSSAEFFVTVAFAFLYSLAATVVVYDFONKYRENNRGP
45	160 170 180 190 200
	NOV6 LVDFCVTVSFTFFWLVAAGKGLTDVKCATRPSSITAAMSVCHGEEAV
	gi 3077703 LVDFCVTVSFTFFWLVAAGKGLTDVKCATRPSSITAAMSVCHGEEAV
	gi 6678874 LVDFCVTVSFTFFWLVAAGKGLTDVKCATRPSSITAAMSVCHGEEAV
	gi 12836843 LIDFIVTVVFSFLWLVGSSAWAKGLSDVKVATDPKEMLLLSACKQPSNK
	gi 1351168 MLDLATAVFAFMWLVSAAWAKGLSDVKVATDPENLIKGMHVCHQPGNT
50	gi 2134413 LIDFIVTVVFSFLWLVGSSAWAKGLSDVKIATDPDEMLLLSACKQPSNK
55	210 220 230 240 250
	NOV6 CSAGATPSMGLANISVLFGFINFELWAGNCWFVFKETPWHGCGCGQDQDQ
	gi 3077703 CSAGATPSMGLANISVLFGFINFELWAGNCWFVFKETPWHGCGCGQ-----
	gi 6678874 CSAGATPSMGLANISVLFGFINFELWAGNCWFVFKETPWHGCGCGQ-----
	gi 12836843 CMAVHSPVMSSLNTSVVFGFLNEILWAGNIWFVFKETGWHSSGQRYLSDP
	gi 1351168 CKELRDPVTSGLNNTSVVFGFLNLVLWVGNLWFVFKETGWAAPFLRAPPGA
	gi 2134413 CLPVRSPVMSSLNTSVVFGFLNEILWAGNIWFVFKETGWHSSGQORHAADT
60	260 270 280 290 300
	NOV6 DQDQ-----GQGP-----SQESAAEQG-----
	gi 3077703 DQDQ-----GQGP-----SQESAAEQG-----
	gi 6678874 DQDQ-----GQGP-----SQESAAEQG-----
	gi 12836843 MEKH-----SSSYNOG--RYN-QESYGSSGGYS-----QQAN-----L
65	gi 1351168 PEKQAPAGDAYGQAGYGQGGYGPQDSYGPQCGYQPDYGPASSGGGGY

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gi|2134413|  M[REDACTED]-----SSGYN[REDACTED]--GYN-[REDACTED]SYGPA[REDACTED]GYN---QPGS-----Y
              310      320
5  NOV6      .....|.....|.....|.....|
gi|3077703|  -----AVEK[REDACTED]
gi|6678874|  -----AVEK[REDACTED]
gi|12836843| GPTSDEFGQQP----SGPTSFN[REDACTED]
10 gi|1351168| GPQG-DYGQGGYGPGAGPTSFSN[REDACTED]
gi|2134413|  GQVG-DYGQPQSYGQSGPTS[REDACTED]

```

Table 6E lists the domain description from DOMAIN analysis results against NOV6. This indicates that the NOV6 sequence has properties similar to those of other proteins known to contain this domain.

Table 6E. Domain Analysis of NOV6	
gnl Pfam pfam01284, Synaptophysin, Synaptophysin / synaptoporin. (SEQ ID NO:103)	
CD-Length = 298 residues, 70.8% aligned	
Score = 244 bits (622), Expect = 6e-66	

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NOV 5: 29  RRLEEPLGFIKVLQWLFAIFAFGSCGSYSGETGAMVRCNNEAKDVSSIIVAFGYPPFRLHR 88
                + |||+|||+|||+|||+|| ||| | | + + + | + | |||
20 Sbjct: 3  MVIFAPLGFVKVLQWVFAIFAFATCGGYSSELQLSVDCAKNTESDLNIDIAFAYPPFRLHE 62
NOV 5: 89  IQYEMPLCDEESSKTMHLMGDFSAPAEFFVTLGIFSFFYTMAALVIYLRFHNLTYTENKR 148
                + + | | | | + | + | + | ||| + + | + | + | | | +
25 Sbjct: 63  VTFEAPTC-EGDEKKNIALVGDSSSAEFFVTVAVFALYSLAALATYIFFQNKYRENNK 121
NOV 5: 149 FPLVDFCVTVSFTFFFWLVAAAAGWGLTQVKGATRPSSLTAAMSVCHEEAVCSAGATPS 208
                ||+|| | | | ++|||+||| || | + | || |
Sbjct: 122  GPLIDFIATAVFALWLVGSSAWAKGLSDVKMATDPEEIKGMHACHQPGNKCKELHDPV 181
30 NOV 5: 209 MGLANISVLFGFINFFLWAGNCWFVKETPWH 240
                | | ||+|||+||| ||| ||| |||
Sbjct: 182  MSGLNLSVVFGFLNFILWAGNIWFVKETGWA 213

```

In skeletal muscle, excitation-contraction (E-C) coupling requires the conversion of the depolarization signal of the invaginated surface membrane, namely the transverse (T-) tubule, to Ca²⁺ release from the sarcoplasmic reticulum (SR) (Takeshima H et al., Biochem J 1998 Apr 1;331 (Pt 1):317-22 / PMID: 9512495, UI: 98180964). Signal transduction occurs at the junctional complex between the T-tubule and SR, designated as the triad junction, which contains two components essential for E-C coupling, namely the dihydropyridine receptor as the T-tubular voltage sensor and the ryanodine receptor as the SR Ca²⁺-release channel. However, functional expression of the two receptors seemed to constitute neither the signal-transduction system nor the junction between the surface and intracellular membranes in cultured cells, suggesting that some as-yet-unidentified molecules participate in both the machinery. In addition, the molecular basis of the formation of the triad junction is totally

unknown. It is therefore important to examine the components localized to the triad junction. Takeshima et al. report the identification using monoclonal antibody and primary structure by cDNA cloning of mitsugumin29, a novel transmembrane protein from the triad junction in skeletal muscle. This protein is homologous in amino acid sequence and shares characteristic structural features with the members of the synaptophysin family. The subcellular distribution and protein structure suggest that mitsugumin29 is involved in communication between the T-tubular and junctional SR membranes.

Physiological roles of the members of the synaptophysin family, carrying four transmembrane segments and being basically distributed on intracellular membranes including synaptic vesicles, have not been established yet (Nishi M et al., J Cell Biol 1999 Dec 27;147(7):1473-80 / PMID: 10613905, UI: 20082885). Recently, mitsugumin29 (MG29) was identified as a novel member of the synaptophysin family from skeletal muscle. MG29 is expressed in the junctional membrane complex between the cell surface transverse (T) tubule and the sarcoplasmic reticulum (SR), called the triad junction, where the depolarization signal is converted to Ca^{2+} release from the SR. In this study, Nishi et al. examined biological functions of MG29 by generating knockout mice. The MG29-deficient mice exhibited normal health and reproduction but were slightly reduced in body weight. Ultrastructural abnormalities of the membranes around the triad junction were detected in skeletal muscle from the mutant mice, i.e., swollen T tubules, irregular SR structures, and partial misformation of triad junctions. In the mutant muscle, apparently normal tetanus tension was observed, whereas twitch tension was significantly reduced. Moreover, the mutant muscle showed faster decrease of twitch tension under Ca^{2+} -free conditions. The morphological and functional abnormalities of the mutant muscle seem to be related to each other and indicate that MG29 is essential for both refinement of the membrane structures and effective excitation-contraction coupling in the skeletal muscle triad junction. These results further imply a role of MG29 as a synaptophysin family member in the accurate formation of junctional complexes between the cell surface and intracellular membranes.

The temporal appearance and subcellular distribution of mitsugumin29 (MG29), a 29-kDa transmembrane protein isolated from the triad junction in skeletal muscle, were examined by immunohistochemistry during the development of rabbit skeletal muscle (Komazaki S et al., Dev Dyn 1999 Jun;215(2):87-95 / PMID: 10373013, UI: 99300228). MG29 appeared in the sarcoplasmic reticulum (SR) in muscle cells at fetal day 15 before the onset of transverse tubule (T tubule) formation. In muscle cells at fetal day 27, in which T tubule and triad formation is ongoing, both SR and triad were labeled for MG29. In muscle cells at newborn 1

day, the labeling of the SR had become weak and the triads were well developed and clearly labeled for MG29. Specific and clear labeling for MG29 was restricted to the triads in adult skeletal muscle cells. When MG29 was expressed in amphibian embryonic cells by injection of the cRNA, a large quantity of tubular smooth-surfaced endoplasmic reticulum (sER) was formed in the cytoplasm. The tubular sER was 20-40 nm in diameter and appeared straight or reticular in shape. The tubular sER was formed by the fusion of coated vesicles [budded off from the rough-surfaced endoplasmic reticulum (rER)] and vacuoles of rER origin. The present results suggest that MG29 may play important roles both in the formation of the SR and the construction of the triads during the early development of skeletal muscle cells.

Recently mitsugumin29 unique to the triad junction in skeletal muscle was identified as a novel member of the synaptophysin family; the members of this family have four transmembrane segments and are distributed on intracellular vesicles. In this study, Shimuta et al. FEBS Lett 1998 Jul 17;431(2):263-7 / PMID: 9708916, UI: 98372647, isolated and analyzed mouse mitsugumin29 cDNA and genomic DNA containing the gene. The mitsugumin29 gene mapped to the mouse chromosome 3 F3-H2 is closely related to the synaptophysin gene in exon-intron organization, which indicates their intimate relationship in molecular evolution. RNA blot hybridization and immunoblot analysis revealed that mitsugumin29 is expressed abundantly in skeletal muscle and at lower levels in the kidney. Immunofluorescence microscopy demonstrated that mitsugumin29 exists specifically in cytoplasmic regions of the proximal and distal tubule cells in the kidney. The results obtained may suggest that mitsugumin29 is involved in the formation of specialized endoplasmic reticulum systems in skeletal muscle and renal tubule cells.

The disclosed NOV6 nucleic acid of the invention encoding a MITSUGUMIN29 -like protein includes the nucleic acid whose sequence is provided in Table 6A or a fragment thereof. The invention also includes a mutant or variant nucleic acid any of whose bases may be changed from the corresponding base shown in Table 6A while still encoding a protein that maintains its MITSUGUMIN29 -like activities and physiological functions, or a fragment of such a nucleic acid. The invention further includes nucleic acids whose sequences are complementary to those just described, including nucleic acid fragments that are complementary to any of the nucleic acids just described. The invention additionally includes nucleic acids or nucleic acid fragments, or complements thereto, whose structures include chemical modifications. Such modifications include, by way of nonlimiting example, modified bases, and nucleic acids whose sugar phosphate backbones are modified or derivatized. These modifications are carried out at least in part to enhance the chemical

stability of the modified nucleic acid, such that they may be used, for example, as antisense binding nucleic acids in therapeutic applications in a subject. In the mutant or variant nucleic acids, and their complements, up to about 10 percent of the bases may be so changed.

5 The disclosed NOV6 protein of the invention includes the MITSUGUMIN29 -like protein whose sequence is provided in Table 6B. The invention also includes a mutant or variant protein any of whose residues may be changed from the corresponding residue shown in Table 6B while still encoding a protein that maintains its MITSUGUMIN29-like activities and physiological functions, or a functional fragment thereof. In the mutant or variant protein, up to about 10 percent of the residues may be so changed.

10 The NOV6 nucleic acids and proteins of the invention are useful in potential therapeutic applications implicated in eye/lens disorders including but not limited to muscular dystrophy, Lesch-Nyhan syndrome, myasthenia gravis, diabetes, autoimmune disease, renal artery stenosis, interstitial nephritis, glomerulonephritis, polycystic kidney disease, systemic lupus erythematosus, renal tubular acidosis, IgA nephropathy, hypercalcaemia,
15 cardiomyopathy, atherosclerosis, hypertension, congenital heart defects, aortic stenosis, atrial septal defect (ASD), atrioventricular (A-V) canal defect, ductus arteriosus, pulmonary stenosis, subaortic stenosis, ventricular septal defect (VSD), valve diseases, tuberous sclerosis, scleroderma, obesity, transplantation, adrenoleukodystrophy, congenital adrenal hyperplasia, and other diseases, disorders and conditions of the like. Also since the invention is highly
20 expressed in one of the lung cancer cell lines (Lung cancer NCI-H522), it may be useful in diagnosis and treatment of this cancer. The NOV6 nucleic acid, or fragments thereof, may further be useful in diagnostic applications, wherein the presence or amount of the nucleic acid or the protein are to be assessed.

NOV6 nucleic acids and polypeptides are further useful in the generation of antibodies
25 that bind immunospecifically to the novel substances of the invention for use in therapeutic or diagnostic methods. These antibodies may be generated according to methods known in the art, using prediction from hydrophobicity charts, as described in the "Anti-NOVX Antibodies" section below. For example the disclosed NOV6 protein have multiple hydrophilic regions, each of which can be used as an immunogen. In one embodiment, contemplated NOV6
30 epitope is from about amino acids 10 to 40. In other embodiments, NOV6 epitope is from about amino acids 60 to 70, from about amino acids 90 to 130, from about amino acids 145 to 155, from about amino acid 170 to 180, and from about amino acids 220 to 270. This novel protein also has value in development of powerful assay system for functional analysis of

various human disorders, which will help in understanding of pathology of the disease and development of new drug targets for various disorders.

NOV7

5 A disclosed NOV7 nucleic acid of 1020 nucleotides (also referred to as 106973211_EXT) encoding a novel Wnt-15-like protein is shown in Table 7A. An open reading frame was identified beginning with an CTG initiation codon at nucleotides 2-4 and ending with a TAG codon at nucleotides 995-997. A putative untranslated region upstream from the initiation codon and downstream from the termination codon is underlined in Table 7A, and the start and stop codons are in bold letters. Since the starting codon is not a traditional initiation codon, NOV7 could represent a partial reading frame, and could further extend in the 5' direction.

Table 7A. NOV7 Nucleotide Sequence (SEQ ID NO:19)

CCTGACCGGGCGGGAAGTCCTGACGCCCTTCCAGGATTGGGCACTGCGGCAGCCCCGGCA CAGGGCGGG
GCCACCTGAAGCAGTGTGACCTGCTGAAGCTGTCCCGGCGGCAGAGCAGCTCTGCCGAGGGAGCCCCG
GCCTGGCTGAGACCTGAGGGATGCTGCGCACCTCGGCCCTGCTTGAGTGCCAGTTTCAGTTCGGGCATGA
GCGCTGGAACTGTAGCCTGGAGGGCAGGATGGGCCTGCTCAAGAGAGGGCTTCAAAGAGACAGCTTTCCTG
TACGCGGTGTCTCTGCCGCCCTCACCCACACCTGGCCCGGGCCTGCAGCGCTGGGCGTGGAGCGCT
GCACCTGTGATGACTCTCCGGGGCTGGAGAGCCGGCAGGCCTGGCAGTGGGGCGTGTGCGGTGACAACCT
CAAGTACAGCACCAAGTTTCTGAGCAACTTCTGGGGTCCAAGAGAGGAAACAAGGACCTGCGGGCACGG
GCAGACGCCCACAATACCCACGTGGGCATCAAGGCTGTGAAGAGTGGCCTCAGGACCACGTGTAAGTGCC
ATGGCGTATCAGGCTCCTGTGCCGTGCGCACCTGCTGGAAGCAGCTCTCCCCGTTCCGTGAGACGGGCCA
GGTGCTGAAACTGCGCTATGACTCGGCTGTCAAGGTGTCCAGTGCCACCAATGAGGCCTTGGGCCCGCTA
GAGCTGTGGGCCCCCTGCCAGGCAGGGCAGCCTACCAAAGGCCTGGCCCCAAGGTCTGGGGACCTGGTGT
ACATGGAGGACTCACCCAGTTCTGCCGGCCAGCAAGTACTCACCTGGCACAGCAGGTAGGGTGTGCTC
CCGGGAGGCCAGCTGCAGCAGCCTGTGCTGCGGGCGGGGCTATGACACCCAGAGCCGCTGGTGGCCTTC
TCCTGCCACTGCCAGGTGCAGTGGTGTGCTACGTGGAGTGCCAGCAATGTGTGCAGGAGGAGCTGTGT
ACACCTGCAAGCACTAGGCCTACTGCCAGCAAGCCAGTC

15 The disclosed NOV7 nucleic acid sequence , located on chromosome 17, has 688 of 1009 bases (68%) identical to a gb:GENBANK-ID:AF031168|acc:AF031168.1 mRNA from *Gallus gallus* (*Gallus gallus* Wnt-14 protein (Wnt-14) mRNA, complete cds) ($E = 3.0e^{-76}$).

A disclosed NOV7 polypeptide (SEQ ID NO:20) encoded by SEQ ID NO:19 is 331 amino acid residues and is presented using the one-letter amino acid code in Table 7B. Signal P, Psort and/or Hydropathy results predict that NOV7 contains no signal peptide and is likely to be localized in the cytoplasm with a certainty of 0.4500. In other embodiments, NOV7 is also likely to be localized to the microbody (peroxisome) with a certainty of 0.3000, the mtochondrial matrix space with a certainty of 0.1000, or to the lysosome (lumen) with a certainty of 0.1000.

Table 7B. Encoded NOV7 protein sequence (SEQ ID NO:20).

LTGREVLTPFPGLGTAAPAQGGAHKQCDDLKLSRRQQLCRREPGLAETLRDAAHLGGLLECQFQFRHERWNCS
LEGRMGLLKRGFKETAFLYAVSSAALHTLARACSAGRMRCTCDDSPGLESRQAWQWGVCGDNLKYSTKFLSNF
LGSKRGNKDLRARADAHNTHVGIKAVKSGSLRTTCKCHGVSGSCAVRTCWKQLSPFRETGQVLKLRYSDAVKVSSA
TNEALGRLELWAPARQGSGLTKGLAPRSGDLVYMEDSPSFCRPSKYSPTAGRVCSREASCSSLCCGRGYDTQSRL
VAFSCHCQVQWCCYVECCQCVQEELVYTCKH

The disclosed NOV7 amino acid sequence has 205 of 330 amino acid residues (62%) identical to, and 252 of 330 amino acid residues (76%) similar to, the 354 amino acid residue ptnr:SWISSPROT-ACC:O42280 protein from *Gallus gallus* (Chicken) (WNT-14 Protein Precursor) ($E = 1.3e^{-114}$).

The tissue expression of NOV7 is predicted to be expressed in brain because of the expression pattern of (GENBANK-ID: gb:GENBANK-ID:AF031168|acc:AF031168.1) a closely related *Gallus gallus* Wnt-14 protein (Wnt-14) mRNA, complete cds homolog.

NOV7 also has homology to the amino acid sequences shown in the BLASTP data listed in Table 7C.

Table 7C. BLAST results for NOV7

Gene Index/ Identifier	Protein/ Organism	Length (aa)	Identity (%)	Positives (%)	Expect
gi 16303264 dbj BAB70499.1 (AB063483)	WNT14B [Homo sapiens]	357	330/331 (99%)	330/331 (99%)	e-175
gi 3915306 sp O42280 WN14_CHICK	WNT-14 PROTEIN PRECURSOR	354	204/332 (61%)	253/332 (75%)	e-109
gi 15082261 ref NP_003386.1 (NM_003395)	wingless-type MMTV integration site family, member 14 [Homo sapiens]	365	209/335 (62%)	255/335 (75%)	e-108
gi 139748 sp P10108 WNT1_XENLA	WNT-1 PROTEIN PRECURSOR (XWNT-1) (XINT-1)	371	120/313 (38%)	175/313 (55%)	5e-58
gi 3024851 sp O14905 WN15_HUMAN	WNT-15 PROTEIN	120	120/120 (100%)	120/120 (100%)	2e-56

The homology of these sequences is shown graphically in the ClustalW analysis shown in Table 7D.

Table 7D Information for the ClustalW proteins

- 1) NOV7 (SEQ ID NO:20)
- 2) gi|16303264|dbj|BAB70499.1| (AB063483) WNT14B [Homo sapiens] (SEQ ID NO:62)
- 3) gi|3915306|sp|O42280|WN14_CHICK WNT-14 PROTEIN PRECURSOR (SEQ ID NO:63)
- 4) gi|15082261|ref|NP_003386.1| (NM_003395) wingless-type MMTV integration site family, member 14 [Homo sapiens] (SEQ ID NO:64)
- 5) gi|139748|sp|P10108|WNT1_XENLA WNT-1 PROTEIN PRECURSOR (XWNT-1) (XINT-1) (SEQ ID NO:65)
- 6) gi|3024851|sp|O14905|WN15_HUMAN WNT-15 PROTEIN (SEQ ID NO:66)

NOV7

.....10.....20.....30.....40.....50

-----LTGRE-----VLTFPFGL

5	gi 16303264	-----MRPPPALALAGLC ⁵⁵ LLALPAA ⁶⁰ AS ⁶⁵ YFGLTGRE-----VLT ⁷⁰ PP ⁷⁵ PGL
	gi 3915306	-----MALLRALLG--L ⁵⁵ ACTPRPSA ⁶⁰ AYFGLTNE-----ALT ⁷⁰ ILP-L
	gi 15082261	MLDGSPLARWLA ⁵⁵ AFGLTLLA ⁶⁰ ALRPSA ⁶⁵ AYFGLTSE-----PL ⁷⁰ TILP-L
	gi 139748	-----MRILTFLGLK ⁵⁵ TLWVLA ⁶⁰ FSSLS ⁶⁵ NTIAV ⁷⁰ NSGK ⁷⁵ WGI ⁸⁰ NVASAG
	gi 3024851	-----
10	NOV760.....70.....80.....90.....100
	gi 16303264	GTAAAP ⁵⁵ AQGG ⁶⁰ AHLK ⁶⁵ CDLL ⁷⁰ KL ⁷⁵ SR ⁸⁰ RQ ⁸⁵ KQL ⁹⁰ CR ⁹⁵ REP ¹⁰⁰ CLA ¹⁰⁵ ETL ¹¹⁰ RDA ¹¹⁵ AH ¹²⁰ GL ¹²⁵ LEC
	gi 3915306	GTAAAP ⁵⁵ AQGG ⁶⁰ AHLK ⁶⁵ CDLL ⁷⁰ KL ⁷⁵ SR ⁸⁰ RQ ⁸⁵ KQL ⁹⁰ CR ⁹⁵ REP ¹⁰⁰ CLA ¹⁰⁵ ETL ¹¹⁰ RDA ¹¹⁵ AH ¹²⁰ GL ¹²⁵ LEC
	gi 15082261	TSEMEEA ⁵⁵ AVKA ⁶⁰ HYKV ⁶⁵ CDRL ⁷⁰ KL ⁷⁵ EKK ⁸⁰ ORM ⁸⁵ CRRD ⁹⁰ PCGA ⁹⁵ ETL ¹⁰⁰ ME ¹⁰⁵ AI ¹¹⁰ SSA ¹¹⁵ LE ¹²⁰ C
	gi 139748	NVLPGSDAR ⁵⁵ PVPL ⁶⁰ VLDPS ⁶⁵ LQL ⁷⁰ LS ⁷⁵ RQ ⁸⁰ KRI ⁸⁵ IRON ⁹⁰ PCIL ⁹⁵ OSI ¹⁰⁰ TRL ¹⁰⁵ HS ¹¹⁰ AI ¹¹⁵ REC
	gi 3024851	-----
20	NOV7110.....120.....130.....140.....150
	gi 16303264	QFQFRHER ¹⁰⁵ WNCS ¹¹⁰ LEG--RMG--LLKRG ¹¹⁵ FKETA ¹²⁰ FLYA ¹²⁵ VSSA ¹³⁰ AAL ¹³⁵ TH ¹⁴⁰ IL ¹⁴⁵ ARAC
	gi 3915306	QFQFRHER ¹⁰⁵ WNCS ¹¹⁰ LEG--RTG--LLKRG ¹¹⁵ FKETA ¹²⁰ FLYA ¹²⁵ VSSA ¹³⁰ AAL ¹³⁵ TH ¹⁴⁰ IL ¹⁴⁵ ARAC
	gi 15082261	QFQFRFER ¹⁰⁵ WNCT ¹¹⁰ LECR ¹¹⁵ YRAS--LLKRG ¹²⁰ FKETA ¹²⁵ FLYA ¹³⁰ ISSA ¹³⁵ GL ¹⁴⁰ THA ¹⁴⁵ MA ¹⁵⁰ KAC
	gi 139748	KWHFRNR ¹⁰⁵ RWNC ¹¹⁰ PTGT ¹¹⁵ GNQ ¹²⁰ VFG ¹²⁵ KI ¹³⁰ INRC ¹³⁵ RETA ¹⁴⁰ VF ¹⁴⁵ AIT ¹⁵⁰ SAG ¹⁵⁵ VTH ¹⁶⁰ SVAR ¹⁶⁵ SC
	gi 3024851	-----
30	NOV7160.....170.....180.....190.....200
	gi 16303264	SAGRMER ¹⁵⁵ CTCDD ¹⁶⁰ SPGLE ¹⁶⁵ SR ¹⁷⁰ QAWQ ¹⁷⁵ WGV ¹⁸⁰ CGD ¹⁸⁵ NLY ¹⁹⁰ ST ¹⁹⁵ KFL ²⁰⁰ SN ²⁰⁵ FLG ²¹⁰ SK ²¹⁵ RGN ²²⁰ KD
	gi 3915306	SAGRMER ¹⁵⁵ CTCDD ¹⁶⁰ SPGLE ¹⁶⁵ SR ¹⁷⁰ QAWQ ¹⁷⁵ WGV ¹⁸⁰ CGD ¹⁸⁵ NLY ¹⁹⁰ ST ¹⁹⁵ KFL ²⁰⁰ SN ²⁰⁵ FLG ²¹⁰ SK ²¹⁵ RGN ²²⁰ KD
	gi 15082261	SAGRMER ¹⁵⁵ CTCDE ¹⁶⁰ APDLEN ¹⁶⁵ REAWQ ¹⁷⁰ WGG ¹⁷⁵ CGD ¹⁸⁰ NLY ¹⁸⁵ SN ¹⁹⁰ KFV ¹⁹⁵ KE ²⁰⁰ FLG ²⁰⁵ -RK ²¹⁰ PN ²¹⁵ KD
	gi 139748	SAGRMER ¹⁵⁵ CTCDE ¹⁶⁰ APDLEN ¹⁶⁵ REAWQ ¹⁷⁰ WGG ¹⁷⁵ CGD ¹⁸⁰ NLY ¹⁸⁵ SS ¹⁹⁰ KFV ¹⁹⁵ KE ²⁰⁰ FLG ²⁰⁵ -RR ²¹⁰ SS ²¹⁵ KD
	gi 3024851	SEGSTES ¹⁵⁵ CS ¹⁶⁰ CDYRR ¹⁶⁵ RGPG ¹⁷⁰ GD ¹⁷⁵ WH ¹⁸⁰ GG ¹⁸⁵ CS ¹⁹⁰ DNIE ¹⁹⁵ GR ²⁰⁰ FIG ²⁰⁵ RE ²¹⁰ FV ²¹⁵ DS ²²⁰ SER ²²⁵ GRD
	gi 3024851	-----
40	NOV7210.....220.....230.....240.....250
	gi 16303264	LRARADA ²⁰⁵ H ²¹⁰ NT ²¹⁵ HV ²²⁰ GI ²²⁵ KAV ²³⁰ KSG ²³⁵ IR ²⁴⁰ TTCK ²⁴⁵ CHG ²⁵⁰ VSG ²⁵⁵ SCA ²⁶⁰ V ²⁶⁵ RT ²⁷⁰ CW ²⁷⁵ QOL ²⁸⁰ SP ²⁸⁵ FRET ²⁹⁰ G
	gi 3915306	LRARADA ²⁰⁵ H ²¹⁰ NT ²¹⁵ HV ²²⁰ GI ²²⁵ KAV ²³⁰ KSG ²³⁵ IR ²⁴⁰ TTCK ²⁴⁵ CHG ²⁵⁰ VSG ²⁵⁵ SCA ²⁶⁰ V ²⁶⁵ RT ²⁷⁰ CW ²⁷⁵ QOL ²⁸⁰ SP ²⁸⁵ FRET ²⁹⁰ G
	gi 15082261	LRARVDF ²⁰⁵ H ²¹⁰ NNL ²¹⁵ VG ²²⁰ KV ²²⁵ IKAG ²³⁰ VETT ²³⁵ CK ²⁴⁰ CHG ²⁴⁵ VSG ²⁵⁰ SCT ²⁵⁵ V ²⁶⁰ RT ²⁶⁵ CW ²⁷⁰ QOL ²⁷⁵ AP ²⁸⁰ HE ²⁸⁵ VG
	gi 139748	LKYLVL ²⁰⁵ NL ²¹⁰ HNN ²¹⁵ QAG ²²⁰ RLT ²²⁵ ML ²³⁰ TEM ²³⁵ RQ ²⁴⁰ ECK ²⁴⁵ CHG ²⁵⁰ MSG ²⁵⁵ CS ²⁶⁰ SL ²⁶⁵ RT ²⁷⁰ CW ²⁷⁵ MRL ²⁸⁰ PP ²⁸⁵ RS ²⁹⁰ SVG
	gi 3024851	-----SGSCA ²⁶⁰ V ²⁶⁵ RT ²⁷⁰ CW ²⁷⁵ QOL ²⁸⁰ SP ²⁸⁵ FRET ²⁹⁰ G
50	NOV7260.....270.....280.....290.....300
	gi 16303264	QVLK ²⁵⁵ LRYD ²⁶⁰ SA ²⁶⁵ VKV ²⁷⁰ SSAT ²⁷⁵ NEAL ²⁸⁰ CR ²⁸⁵ LEL ²⁹⁰ WAP ²⁹⁵ AR---QGS ³⁰⁰ LT ³⁰⁵ KGL ³¹⁰ AP ³¹⁵ RS ³²⁰ GDLV
	gi 3915306	QVLK ²⁵⁵ LRYD ²⁶⁰ SA ²⁶⁵ VKV ²⁷⁰ SSAT ²⁷⁵ NEAL ²⁸⁰ CR ²⁸⁵ LEL ²⁹⁰ WAP ²⁹⁵ AR---QGS ³⁰⁰ LT ³⁰⁵ KGL ³¹⁰ AP ³¹⁵ RS ³²⁰ GDLV
	gi 15082261	KOLK ²⁵⁵ QYET ²⁶⁰ SL ²⁶⁵ KV ²⁷⁰ GST ²⁷⁵ TNEA ²⁸⁰ TCE ²⁸⁵ -GDI ²⁹⁰ SP ²⁹⁵ PK--KSI ³⁰⁰ PGH ³⁰⁵ SD ³¹⁰ QI ³¹⁵ PR ³²⁰ TD ³²⁵ LV
	gi 139748	KHLK ²⁵⁵ HYET ²⁶⁰ AL ²⁶⁵ KV ²⁷⁰ GST ²⁷⁵ TNEA ²⁸⁰ AGEA ²⁸⁵ GIS ²⁹⁰ PP ²⁹⁵ GRAS ³⁰⁰ CAG ³⁰⁵ SD ³¹⁰ PL ³¹⁵ PR ³²⁰ PE ³²⁵ LV
	gi 3024851	DALKD ²⁵⁵ RED ²⁶⁰ GASK ²⁶⁵ VITY ²⁷⁰ SN ²⁷⁵ NGS ²⁸⁰ NR ²⁸⁵ WGS ²⁹⁰ RS ²⁹⁵ DPH--LE ³⁰⁰ PEN ³⁰⁵ PTH ³¹⁰ AL ³¹⁵ PS ³²⁰ SQ ³²⁵ DLV
60	NOV7310.....320.....330.....340.....350
	gi 16303264	YMEDSP ³⁰⁵ SFC ³¹⁰ RP ³¹⁵ SKYS--PGT ³²⁰ AGR ³²⁵ VCS ³³⁰ RE---ASC ³³⁵ SSL ³⁴⁰ CC ³⁴⁵ GR ³⁵⁰ GY ³⁵⁵ DT ³⁶⁰ QSR ³⁶⁵ I
	gi 3915306	YMEDSP ³⁰⁵ SFC ³¹⁰ RP ³¹⁵ SKYS--PGT ³²⁰ AGR ³²⁵ VCS ³³⁰ RE---ASC ³³⁵ SSL ³⁴⁰ CC ³⁴⁵ GR ³⁵⁰ GY ³⁵⁵ DT ³⁶⁰ QSR ³⁶⁵ I
	gi 15082261	YIDDSP ³⁰⁵ SFCL ³¹⁰ MS ³¹⁵ RY ³²⁰ S--PGT ³²⁵ SGR ³³⁰ KCY ³³⁵ KL---KN ³⁴⁰ CD ³⁴⁵ SI ³⁵⁰ CC ³⁵⁵ GR ³⁶⁰ GH ³⁶⁵ NT ³⁷⁰ QSR ³⁷⁵ V
	gi 139748	HLLDSP ³⁰⁵ SFCL ³¹⁰ AG ³¹⁵ RES--PGT ³²⁰ AGR ³²⁵ RC ³³⁰ HE---KN ³³⁵ CE ³⁴⁰ SI ³⁴⁵ CC ³⁵⁰ GR ³⁵⁵ GH ³⁶⁰ NT ³⁶⁵ QSR ³⁷⁰ V
	gi 3024851	YFEKSP ³⁰⁵ NFC ³¹⁰ SP ³¹⁵ SKNG ³²⁰ TPGT ³²⁵ IG ³³⁰ RI ³³⁵ CN ³⁴⁰ ST ³⁴⁵ SL ³⁵⁰ GL ³⁵⁵ DG ³⁶⁰ CEL ³⁶⁵ LCC ³⁷⁰ GR ³⁷⁵ GY ³⁸⁰ SL ³⁸⁵ FE ³⁹⁰ K
65	NOV7360.....370.....380
	gi 16303264	VAFSCH ³⁵⁵ CQ ³⁶⁰ VQ ³⁶⁵ WCC ³⁷⁰ YVE ³⁷⁵ CQ ³⁸⁰ QV ³⁸⁵ OE ³⁹⁰ EL ³⁹⁵ VYT ⁴⁰⁰ CKH
	gi 3915306	VAFSCH ³⁵⁵ CQ ³⁶⁰ VQ ³⁶⁵ WCC ³⁷⁰ YVE ³⁷⁵ CQ ³⁸⁰ QV ³⁸⁵ OE ³⁹⁰ EL ³⁹⁵ VYT ⁴⁰⁰ CKH
	gi 15082261	VTRPC ³⁵⁵ CQ ³⁶⁰ VR ³⁶⁵ WCC ³⁷⁰ YVE ³⁷⁵ CQ ³⁸⁰ QTO ³⁸⁵ REE ³⁹⁰ VYT ³⁹⁵ CKD
	gi 139748	VTRPC ³⁵⁵ CQ ³⁶⁰ VR ³⁶⁵ WCC ³⁷⁰ YVE ³⁷⁵ CQ ³⁸⁰ QTO ³⁸⁵ REE ³⁹⁰ VYT ³⁹⁵ CKG
	gi 3024851	VTERCH ³⁵⁵ CT ³⁶⁰ FN ³⁶⁵ WCC ³⁷⁰ HT ³⁷⁵ CL ³⁸⁰ NT ³⁸⁵ SS ³⁹⁰ QIV ³⁹⁵ HE ⁴⁰⁰ CL-
	gi 3024851	VAFSCHCQV-----

Tables 7E and 7F list the domain descriptions from DOMAIN analysis results against NOV7. This indicates that the NOV7 sequence has properties similar to those of other proteins known to contain this domain.

5

Table 7E. Domain Analysis of NOV7

gnl|Pfam|pfam00110, wnt, wnt family. (SEQ ID NO:104)
CD-Length = 313 residues, 97.8% aligned
Score = 268 bits (684), Expect = 5e-73

NOV 6:	34	LSRRQKQLCRREPGLAETLRDAAHLGLECQFQFRHERWNC	SLEGRMGL-----LKR	GFK	88
Sbjct:	8	LSPRQRQLCRRNPDMASVSEGAQLAIQECQHFRGRRWNC	STLDRLRVVFGKVLKKGTR		67
NOV 6:	89	ETAFLYAVSSAALHTLARACSAGRMERCTCDDSPG-LES	RQAWQWGVCGDNLKYSTKFL		147
Sbjct:	68	ETAFVYAISSAGVAHAVTRACSEGELESCGCDYKKGPG	PGSQSWQGGCSDNVEFGIRFS		127
NOV 6:	148	SNFLGSKRGNKDLRARADAHNTHVGIAVKSGSLRTTCK	CHGVSGSCAVRTCWKQLSPFRE		207
Sbjct:	128	REFVDARERERDARSLMNLHNEAGRAVKASHMRRECK	CHGVSGSCSMKTCWLSLPDFRA		187
NOV 6:	208	TGQVLKLRYSADKVVSSATNEALGRLELWAPARQGS	LTGKLAPRSGDLVYMEDSPSFCR-		266
Sbjct:	188	VGDALKDKYDGAIRV--EPNKRGMGQGSAPRLVAKN	PRFKPPTPSDLVYLEDSPDYCER		244
NOV 6:	267	-PSKSPGTAGRVCSREA---SCSSLCGGRGYDTQSRL	VAFSCHCQVQWCCYVECCQCV		321
Sbjct:	245	DRSTGSLGTQGRVCNKTSKGLDGCCELLCCGRGYNT	QQVERTEKCNCKFHWCCYVKCEECQ		304
NOV 6:	322	QEELVYTCK	330		
Sbjct:	305	EVVEVHTCK	313		

30

Table 7F. Domain Analysis of NOV7

gnl|Smart|smart00097, WNT1, found in Wnt-1 (SEQ ID NO:105)
CD-Length = 304 residues, 98.7% aligned
Score = 248 bits (632), Expect = 5e-67

NOV 6:	34	LSRRQKQLCRREPGLAETLRDAAHLGLECQFQFRHERWNC	SLEGRMGL-----LKR	GFK	89
Sbjct:	5	LSRRQRQLCRANPDVMAVSEGAQEGIEECQHFRFRWNC	STAGLASIFGKVLKQGTRE		64
NOV 6:	90	TAFVLYAVSSAALHTLARACSAGRMERCTCDDSPGLE	SRQAWQWGVCGDNLKYSTKFLSN		149
Sbjct:	65	TAFVYAISSAGVAHAVTRACSQGELDSCGCDYSKRG	SGGRGWEWGCSNIDFGIGFSRE		124
NOV 6:	150	FLGSK-RGNKDLRARADAHNTHVGIAVKSGSLRTTCK	CHGVSGSCAVRTCWKQLSPFRET		208
Sbjct:	125	FVDARERRGSDARALMNLHNEAGRLAVKKTMRCKCH	GVSGSCSVKTCWLQLPFREFI		184
NOV 6:	209	GQVLKLRYSADKVVSSATNEALGRLELWAPARQGS	LTGKLAPRSGDLVYMEDSPSFC--R		266
Sbjct:	185	GDYLKEKYDGASEV-VLDKRGTRGLVPANRDFK-----	PPTNTDLVYLESSPDFCEKN		236

45

pathway. Current hypotheses concerning presenilin function are based upon its cellular localization and its putative interaction as macromolecular complexes with the cell-adhesion/signaling beta-catenin molecule and the glycogen synthase kinase 3beta (GSK-3beta) enzyme. Developmental studies have shown that PS proteins function as components in the Notch signal transduction cascade and that beta-catenin and GSK-3beta are transducers of the Wnt signaling pathway. Both pathways are thought to have an important role in brain development, and they have been connected through Dishevelled (Dvl) protein, a known transducer of the Wnt pathway.

Members of the vertebrate Wnt family have been subdivided into two functional classes according to their biological activities. Some Wnts signal through the canonical Wnt-1/wingless pathway by stabilizing cytoplasmic beta-catenin. By contrast other Wnts stimulate intracellular Ca²⁺ release and activate two kinases, CamKII and PKC, in a G-protein-dependent manner. Moreover, putative Wnt receptors belonging to the Frizzled gene family have been identified that preferentially couple to the two prospective pathways in the absence of ectopic Wnt ligand and that might account for the signaling specificity of the Wnt pathways. As Ca²⁺ release was the first described feature of the noncanonical pathway, and as Ca²⁺ probably plays a key role in the activation of CamKII and PKC, Kuhl M, et al., (*Trends Genet* 2000 Jul;16(7):279-83) have named this Wnt pathway the Wnt/Ca²⁺ pathway.

Many constituents of Wnt signaling pathways are expressed in the developing and mature nervous systems. Recent work has shown that Wnt signaling controls initial formation of the neural plate and many subsequent patterning decisions in the embryonic nervous system, including formation of the neural crest. Wnt signaling continues to be important at later stages of development. Wnts have been shown to regulate the anatomy of the neuronal cytoskeleton and the differentiation of synapses in the cerebellum. Wnt signaling has been demonstrated to regulate apoptosis and may participate in degenerative processes leading to cell death in the aging brain.

Recent genetic studies have shown that the signalling factor Wnt3a is required for formation of the hippocampus; the developmental consequences of Wnt signalling in the hippocampus are mediated by multiple HMG-box transcription factors, with LEF-1 being required just for formation of the dentate gyrus.

Wnt-1 was first identified as a protooncogene activated by viral insertion in mouse mammary tumors. Transgenic expression of this gene using a mouse mammary tumor virus LTR enhancer causes extensive ductal hyperplasia early in life and mammary adenocarcinomas in approximately 50% of the female transgenic (TG) mice by 6 months of

age. Metastasis to the lung and proximal lymph nodes is rare at the time tumors are detected but frequent after the removal of the primary neoplasm. The potent mitogenic effect mediated by Wnt-1 expression does not require estrogen stimulation; tumors form after an increased latency in estrogen receptor alpha-null mice. Several genetic lesions, including inactivation of p53 and over-expression of Fgf-3, collaborate with Wnt-1 in leading to mammary tumors, but loss of Sky and inactivation of one allele of Rb do not affect the rate of tumor formation in Wnt-1 TG mice.

Communication between cells is often mediated by secreted signaling molecules that bind cell surface receptors and modulate the activity of specific intracellular effectors. The Wnt family of secreted glycoproteins is one group of signaling molecules that has been shown to control a variety of developmental processes including cell fate specification, cell proliferation, cell polarity and cell migration. In addition, mis-regulation of Wnt signaling can cause developmental defects and is implicated in the genesis of several human cancers. The importance of Wnt signaling in development and in clinical pathologies is underscored by the large number of primary research papers examining various aspects of Wnt signaling that have been published in the past several years.

Reproductive tract development and function is regulated by circulating steroid hormones. In the mammalian female reproductive tract, estrogenic compounds direct many aspects of cytodifferentiation including uterine gland formation, smooth muscle morphology, and epithelial differentiation. While it is clear that these hormones act through their cognate nuclear receptors, it is less clear what signaling events follow hormonal stimulation that govern cytodifferentiation. Recent advances in molecular embryology and cancer cell biology have identified the Wnt family of secreted signaling molecules. Discussed here are recent advances that point to a definitive role during uterine development and adult function for one member of the Wnt gene family, Wnt-7a. In addition, recent data is reviewed that implicates Wnt-7a deregulation in response to pre-natal exposure to the synthetic estrogenic compound, DES. These advances point to an important role for the Wnt gene family in various reproductive tract pathologies including cancer.

Holoprosencephaly (HPE) is the most common developmental defect of the forebrain in humans. Several distinct human genes for holoprosencephaly have now been identified. They include Sonic hedgehog (SHH), ZIC2, and SIX3. Many additional genes involved in forebrain development are rapidly being cloned and characterized in model vertebrate organisms. These include Patched (Ptc), Smoothened (Smo), cubitus interruptus (ci)/Gli, wingless (wg/Wnt, decapentaplegic (dpp)/BMP, Hedgehog interacting protein (Hip), nodal,

Smads, One-eyed pinhead (Oep), and TG-Interacting Factor (TGIF). However, further analysis is needed before their roles in HPE can be established.

Female reproductive hormones control mammary gland morphogenesis. In the absence of the progesterone receptor (PR) from the mammary epithelium, ductal side-branching fails to occur. Briskin C, et al. (*Genes Dev* 2000 Mar 15;14(6):650-4) overcame this defect by ectopic expression of the protooncogene Wnt-1. Transplantation of mammary epithelia from Wnt-4(-)/(-) mice shows that Wnt-4 has an essential role in side-branching early in pregnancy. PR and Wnt-4 mRNAs colocalize to the luminal compartment of the ductal epithelium. Progesterone induces Wnt-4 in mammary epithelial cells and is required for increased Wnt-4 expression during pregnancy. Thus, Wnt signaling is essential in mediating progesterone function during mammary gland morphogenesis.

Synapse formation requires changes in cell morphology and the upregulation and localization of synaptic proteins. In the cerebellum, mossy fibers undergo extensive remodeling as they contact several granule cells and form complex, multisynaptic glomerular rosettes. Hall AC, et al., (*Cell* 2000 Mar 3;100(5):525-35) showed that granule cells secrete factors that induce axon and growth cone remodeling in mossy fibers. This effect is blocked by the WNT antagonist, sFRP-1, and mimicked by WNT-7a, which is expressed by granule cells. WNT-7a also induces synapsin I clustering at remodeled areas of mossy fibers, a preliminary step in synaptogenesis. Wnt-7a mutant mice show a delay in the morphological maturation of glomerular rosettes and in the accumulation of synapsin I. We propose that WNT-7a can function as a synaptogenic factor.

Estrogens have important functions in mammary gland development and carcinogenesis. To better define these roles, Bocchinfuso WP, et al., (*Cancer Res* 1999 Apr 15;59(8):1869-76) have used two previously characterized lines of genetically altered mice: estrogen receptor-alpha (ER alpha) knockout (ERKO) mice, which lack the gene encoding ER alpha, and mouse mammary virus tumor (MMTV)-Wnt-1 transgenic mice (Wnt-1 TG), which develop mammary hyperplasia and neoplasia due to ectopic production of the Wnt-1 secretory glycoprotein. Bocchinfuso WP, et al. have crossed these lines to ascertain the effects of ER alpha deficiency on mammary gland development and carcinogenesis in mice expressing the Wnt-1 transgene. Introduction of the Wnt-1 transgene into the ERKO background stimulates proliferation of alveolar-like epithelium, indicating that Wnt-1 protein can promote mitogenesis in the absence of an ER alpha-mediated response. The hyperplastic glandular tissue remains confined to the nipple region, implying that the requirement for ER alpha in ductal expansion is not overcome by ectopic Wnt-1. Tumors were detected in virgin ERKO

females expressing the Wnt-1 transgene at an average age (48 weeks) that is twice that seen in virgin Wnt-1 TG mice (24 weeks) competent to produce ER alpha. Prepubertal ovariectomy of Wnt-1 TG mice also extended tumor latency to 42 weeks. However, pregnancy did not appear to accelerate the appearance of tumors in Wnt-1 TG mice, and tumor growth rates were not measurably affected by late ovariectomy. Small hyperplastic mammary glands were observed in Wnt-1 TG males, regardless of ER alpha gene status; the glands were similar in appearance to those found in ERKO/Wnt-1 TG females. Mammary tumors also occurred in Wnt-1 TG males; latency tended to be longer in the heterozygous ER alpha and ERKO males (86 to 100 weeks) than in wild-type ER alpha mice (ca. 75 weeks). Bocchinfuso WP, et al. concluded that ectopic expression of the Wnt-1 proto-oncogene can induce mammary hyperplasia and tumorigenesis in the absence of ER alpha in female and male mice. The delayed time of tumor appearance may depend on the number of cells at risk of secondary events in the hyperplastic glands, on the carcinogenesis-promoting effects of ER alpha signaling, or on both.

Wnt-1 and Wnt-3a proto-oncogenes have been implicated in the development of midbrain and hindbrain structures. Evidence for such a role has been derived from in situ hybridization studies showing Wnt-1 and -3a expression in developing cranial and spinal cord regions and from studies of mutant mice whose Wnt-1 genes have undergone targeted disruption by homologous recombination. Wnt-1 null mutants exhibit cranial defects but no spinal cord abnormalities, despite expression of the gene in these regions. The absence of spinal cord abnormalities is thought to be due to a functional compensation of the Wnt-1 deficiency by related genes, a problem that has complicated the analysis of null mutants of other developmental genes as well. Augustine K, et al., (*Dev Genet* 1993;14(6):500-20) describe the attenuation of Wnt-1 expression using antisense oligonucleotide inhibition in mouse embryos grown in culture. Augustine K, et al. induced similar mid- and hindbrain abnormalities as those seen in the Wnt-1 null mutant mice. Attenuation of Wnt-1 expression was also associated with cardiomegaly resulting in hemostasis. These findings are consistent with the possibility that a subset of Wnt-1 expressing cells include neural crest cells known to contribute to septation of the truncus arteriosus and to formation of the visceral arches. Antisense knockout of Wnt-3a, a gene structurally related to Wnt-1, targeted the forebrain and midbrain region, which were hypoplastic and failed to expand, and the spinal cord, which exhibited lateral outpocketings at the level of the forelimb buds. Dual antisense knockouts of Wnt-1 and Wnt-3a targeted all brain regions leading to incomplete closure of the cranial neural folds, and an increase in the number and severity of outpocketings along the spinal cord, suggesting that these genes complement one another to produce normal patterning of the

spinal cord. The short time required to assess the mutant phenotype (2 days) and the need for limited sequence information of the target gene (20-25 nucleotides) make this antisense oligonucleotide/whole embryo culture system ideal for testing the importance of specific genes and their interactions in murine embryonic development.

5 Wnt-1 (previously known as int-1) is a proto-oncogene induced by the integration of the mouse mammary tumor virus. It is thought to play a role in intercellular communication and seems to be a signalling molecule important in the development of the central nervous system (CNS). The sequence of wnt-1 is highly conserved in mammals, fish, and amphibians. Wnt-1 is a member of a large family of related proteins that are all thought to be
10 developmental regulators. These proteins are known as wnt-2 (also known as irp), wnt-3 up to wnt-15. At least four members of this family are present in *Drosophila*. One of them, wingless (wg), is implicated in segmentation polarity. All these proteins share the following features characteristics of secretory proteins, a signal peptide, several potential N-glycosylation sites and 22 conserved cysteines that are probably involved in disulfide bonds. The Wnt proteins
15 seem to adhere to the plasma membrane of the secreting cells and are therefore likely to signal over only few cell diameters.

 The disclosed NOV7 nucleic acid of the invention encoding a Wnt-15-like protein includes the nucleic acid whose sequence is provided in Table 7A or a fragment thereof. The invention also includes a mutant or variant nucleic acid any of whose bases may be changed
20 from the corresponding base shown in Table 7A while still encoding a protein that maintains its Wnt-15-like activities and physiological functions, or a fragment of such a nucleic acid. The invention further includes nucleic acids whose sequences are complementary to those just described, including nucleic acid fragments that are complementary to any of the nucleic acids just described. The invention additionally includes nucleic acids or nucleic acid fragments, or
25 complements thereto, whose structures include chemical modifications. Such modifications include, by way of nonlimiting example, modified bases, and nucleic acids whose sugar phosphate backbones are modified or derivatized. These modifications are carried out at least in part to enhance the chemical stability of the modified nucleic acid, such that they may be used, for example, as antisense binding nucleic acids in therapeutic applications in a subject.
30 In the mutant or variant nucleic acids, and their complements, up to about 32 percent of the bases may be so changed.

 The disclosed NOV7 protein of the invention includes the Wnt-15-like protein whose sequence is provided in Table 7B. The invention also includes a mutant or variant protein any

of whose residues may be changed from the corresponding residue shown in Table 7B while still encoding a protein that maintains its Wnt-15-like activities and physiological functions, or a functional fragment thereof. In the mutant or variant protein, up to about 38 percent of the residues may be so changed.

5 The above defined information for this invention suggests that these Wnt-15-like proteins (NOV7) may function as a member of a “Wnt-15 family”. Therefore, the NOV7 nucleic acids and proteins identified here may be useful in potential therapeutic applications implicated in (but not limited to) various pathologies and disorders as indicated below. The potential therapeutic applications for this invention include, but are not limited to: protein
10 therapeutic, small molecule drug target, antibody target (therapeutic, diagnostic, drug targeting/cytotoxic antibody), diagnostic and/or prognostic marker, gene therapy (gene delivery/gene ablation), research tools, tissue regeneration *in vivo* and *in vitro* of all tissues and cell types composing (but not limited to) those defined here.

 The nucleic acids and proteins of NOV7 are useful in Von Hippel-Lindau (VHL)
15 syndrome, Alzheimer's disease, stroke, tuberous sclerosis, hypercalcaemia, Parkinson's disease, Huntington's disease, cerebral palsy, epilepsy, Lesch-Nyhan syndrome, multiple sclerosis, ataxia-telangiectasia, leukodystrophies, behavioral disorders, addiction, anxiety, pain, neurodegeneration, cancer, developmental defects, and/or other pathologies and disorders. The novel NOV7 nucleic acid encoding NOV7 protein, or fragments thereof, may
20 further be useful in diagnostic applications, wherein the presence or amount of the nucleic acid or the protein are to be assessed. These materials are further useful in the generation of antibodies that bind immunospecifically to the novel substances of the invention for use in therapeutic or diagnostic methods.

 NOV7 nucleic acids and polypeptides are further useful in the generation of antibodies
25 that bind immunospecifically to the novel substances of the invention for use in therapeutic or diagnostic methods. These antibodies may be generated according to methods known in the art, using prediction from hydrophobicity charts, as described in the “Anti-NOVX Antibodies” section below. For example the disclosed NOV7 protein have multiple hydrophilic regions, each of which can be used as an immunogen. In one embodiment, contemplated NOV7
30 epitope is from about amino acids 25 to 60. In other embodiments, NOV7 epitope is from about amino acids 65 to 80, from about amino acids 110 to 140, from about amino acids 145 to 180, from about amino acids 190 to 220, from about amino acids 230 to 270, or from about amino acids 280 to 290. This novel protein also has value in development of powerful assay

system for functional analysis of various human disorders, which will help in understanding of pathology of the disease and development of new drug targets for various disorders.

NOV8

- 5 A disclosed NOV8 nucleic acid of 1085 nucleotides (also referred to 88091010_EXT) encoding a novel Wnt-14-like protein is shown in Table 8A. An open reading frame was identified beginning with an ATG initiation codon at nucleotides 13-15 and ending with a TGA codon at nucleotides 1078-1080. In Table 8A, the 5' and 3' untranslated regions are underlined and the start and stop codons are in bold letters.

10

Table 8A. NOV8 Nucleotide Sequence (SEQ ID NO:21)	
<u>TAGTGAGCCGAGATGGCACTACTATATTCCAGCTTGGGTGTGGTTGTGTGCACCTGTAGTCCTAGTTACTT</u>	
<u>TGGACTGACGGGCAGCGAGCCCCCTGACCATCCTCCGCTGACCCTGGAGCCAGAGGCGGCTGCCACAGGCGC</u>	
<u>ACTACAAGGCCTGCGACCGGCTGAAGCTGGAGCGGAAGCAGCGGCGCATGTGCCGCGGGACCCGGGCGTG</u>	
<u>GCAGAGACGCTGGTGGAGGCCGTGAGCATGAGTGCCTCGAGTGCCAGTTCCAGTTCCGCTTTGAGCGCTG</u>	
<u>GAATGCGACGCTGGAGGGCCGCTACCGGGCCAGCCTGCTCAAGCGAGGTTTCAAGGAGACTGCCTTCCTCT</u>	
<u>ATGCCATCTCCTCGGCTGGCCTGACGCACGCACTGGCCAAGGCGTGACGCGGGGCCGATGGAGCGCTGT</u>	
<u>ACCTGCGATGAGGCACCCGACCTGGAGAACCGTGAGGGCTGGAAGTGGGGTGGCTGTAGCGAGGACATCGA</u>	
<u>GTTTGGTGGGATGGTGTCTCGGGAGTTTCGCCGACGCCCGGGAGAACCGGCCAGATGCCCGCTCAGCCATGA</u>	
<u>ACCGCCACAACAACGAGGCTGGGCGCCAGGTGATCAAGGCTGGGGTGGAGACCCTGCAAGTGCCACGGC</u>	
<u>GTGTCAGGCTCATGCACGGTGCGGACCTGCTGGCGGCAGTTGGCGCCTTTCATGAGGTGGGCAAGCATCT</u>	
<u>GAAGCACAAGTATGAGTCGGCACTCAAGGTGGGCAGCACCAATGAAGCTGCCGGCGAGGCAGGTGCCA</u>	
<u>TCTCCCACCAACGGGGCGTGCTCGGGGGCAGGTGGCAGCGACCCGCTGCCCGCACTCCAGAGCTGGTG</u>	
<u>CACCTGGATGACTCGCCTAGCTTCTGCCTGGCTGGCCGCTTCTCCCCGGGCACCGCTGGCCGTAGGTGCCA</u>	
<u>CCGTGAGAAGAACTGCGAGAGCATCTGCTGTGGCCGCGGCCATAACACAGAGCCGGGTGGTGACAAGGC</u>	
<u>CCTGCCAGTGCCAGGTGCGTTGGTGTCTATGTGAGTGCAGGCAGTGCACGCAGCGTGAGGAGGTCTAC</u>	
<u>ACCTGCAAGGGCTGAGTTCC</u>	

The disclosed NOV8 nucleic acid sequence, localized to chromosome 1, has 560 of 725 bases (77%) identical to a gb:GENBANK-ID:AF031168|acc:AF031168.1 mRNA from *Gallus gallus* (*Gallus gallus* Wnt-14 protein (Wnt-14) mRNA, complete cds (E = 5.2e⁻¹¹⁵).

- 15 A disclosed NOV8 polypeptide (SEQ ID NO:22) encoded by SEQ ID NO:21 is 355 amino acid residues and is presented using the one-letter amino acid code in Table 8B. Signal P, Psort and/or Hydropathy results predict that NOV8 has a signal peptide and is likely to be localized extracellularly with a certainty of 0.3700. In other embodiments, NOV8 is also likely to be localized to the enoplasmic reticulum (membrane) with a certainty of 0.1000, to the
- 20 endoplasmic reticulum (lumen) with a certainty of 0.1000, or the lysosome (lumen) with a certainty of 0.1000. The most likely cleavage site for a NOV8 peptide is between amino acids 15 and 16, at: CTC-SP.

Table 8B. Encoded NOV8 protein sequence (SEQ ID NO:22).	
MALLYSSLGVVVTCSPSYFGLTGSEPLTILPLTLEPEAAAQAHYKACDRLKLERKQRRMCRDPGVAETL	

VEAVSMSALECQFQFRFERWNCTLEGRYRASLLKRGFKETAFLYAIISSAGLTHALAKACSAGRMRCTCDE
APDLENREGWKWGGCSEIEFGGMVSREFADARENRPDARSAMNRHNEAGRQVIKAGVETTCCKHGVSGS
CTVRTCWRQLAPFHEVGKHLKHYESALKVGSTTNEAAGEAGAI SPPRGRASGAGSDPLPRTPELVHLDD
SPSFCLAGRFSPGTAGRRCHREKNCESICCGRGHNTQSRVVTTRPCQCQVRWCCYVECRQCTQREEVYTCCKG

The disclosed NOV8 amino acid sequence has 270 of 354 amino acid residues (76%) identical to, and 310 of 354 amino acid residues (87%) similar to, the 354 amino acid residue ptmr:SWISSPROT-ACC:O42280 protein from *Gallus gallus* (Chicken) (WNT-14 Protein Precursor (1.2e⁻¹⁵¹).

NOV8 is expressed in at least brain. This information was derived by determining the tissue sources of the sequences that were included in the invention including but not limited to SeqCalling sources, Public EST sources, Literature sources, and/or RACE sources.

In addition, the sequence is predicted to be expressed in brain because of the expression pattern of (GENBANK-ID: gb:GENBANK-ID:AF031168|acc:AF031168.1) a closely related [*Gallus gallus* Wnt-14 protein (Wnt-14) mRNA, complete cds].

NOV8 also has homology to the amino acid sequence shown in the BLASTP data listed in Table 8C.

Table 8C. BLAST results for NOV8					
Gene Index/ Identifier	Protein/ Organism	Length (aa)	Identity (%)	Positives (%)	Expect
gi 15082261 ref NP_003386.1 (NM_003395)	wingless-type MMTV integration site family, member 14 [Homo sapiens]	365	306/340 (90%)	321/340 (94%)	e-167
gi 3915306 sp O42280 WN14_CHICK	WNT-14 PROTEIN PRECURSOR	354	270/357 (75%)	310/357 (86%)	e-142
gi 16303264 dbj BAB70499.1 (AB063483)	WNT14B [Homo sapiens]	357	193/339 (56%)	244/339 (71%)	e-100
gi 7106447 ref NP_033548.1 (NM_009522)	wingless-related MMTV integration site 3A [Mus musculus]	352	141/311 (45%)	179/311 (57%)	2e-62
gi 5821261 dbj BAA83743.1 (AB024080)	Wnt-3a [Gallus gallus]	376	139/311 (44%)	179/311 (56%)	3e-62

The homology of these sequences is shown graphically in the ClustalW analysis shown in Table 8D.

Table 8D. Information for the ClustalW proteins

- 1) NOV8 (SEQ ID NO:22)
- 2) gi|15082261|ref|NP_003386.1| (NM_003395) wingless-type MMTV integration site family, member 14 [Homo sapiens] (SEQ ID NO:64)
- 3) gi|3915306|sp|O42280|WN14_CHICK WNT-14 PROTEIN PRECURSOR (SEQ ID NO:63)
- 4) gi|16303264|dbj|BAB70499.1| (AB063483) WNT14B [Homo sapiens] (SEQ ID NO:62)
- 5) gi|7106447|ref|NP_033548.1| (NM_009522) wingless-related MMTV integration site 3A [Mus musculus] (SEQ ID NO:67)
- 6) gi|5821261|dbj|BAA83743.1| (AB024080) Wnt-3a [Gallus gallus] (SEQ ID NO:68)

		10	20	30	40	50
5	NOV8MALLYSGLGVVCT.....CPSYFGLTGSEPLTILF..				
	gi 15082261	MLDGSPLARWLAAPGLTLLAALR.....PSAAVFGLTGSEPLTILF..				
	gi 3915306MALLRLQLLLACTP.....RPSAAVFGLTGSEPLTILF..				
	gi 16303264MRPPPALALAGLCLLALP.....AAAFYFGLTGSEPLTILF..				
	gi 7106447MAPLGYLMLCS.....LKQA.....LG-SYPLWWS.....				
	gi 5821261MKSFCSEVVAKSRGLKQGWCGWTMGSAKKKWISEQRSLLEW				
10		60	70	80	90	100
	NOV8LTLEP-EANACAHYKACDRLK-LERKORRMCRRDPCVAETLVEAVS				
	gi 15082261LTLEP-EANACAHYKACDRLK-LERKORRMCRRDPCVAETLVEAVS				
	gi 3915306LTSEMEBAVKAHYKACDRLK-LERKORRMCRRDPCVAETLVEAVS				
15	gi 16303264LGTAAAPAGGCAHLKCDLKL-SRRQKOLCRREPCLAEPLRFAAH				
	gi 7106447LAVGPQYSSLSTOPILCASHPGLVPKCLRFRCRNYVELMPSVAECVK				
	gi 5821261	DVGSLSLGHQYSSLGTQPILCGSLPGLVPKCLRFRCRNYVELMPSVAECVK				
20		110	120	130	140	150
	NOV8	MSALECCQFRFRERWNTLEGR---YRASLLKRGFKETAFLYAISSAGLT				
	gi 15082261	MSALECCQFRFRERWNTLEGR---YRASLLKRGFKETAFLYAISSAGLT				
	gi 3915306	MSALECCQFRFRERWNTLEGR---YRASLLKRGFKETAFLYAISSAGLT				
25	gi 16303264	LGLLECCQFRFRERWNTLEGR---RTGLLKRGFKETAFLYAISSAGLT				
	gi 7106447	AGIQECCQFRFRERWNTTVNSLAIIFGPVLDKATRESAFVHAIASAGVA				
	gi 5821261	LGIQECCQFRFRERWNTTVNSLAIIFGPVLDKATRESAFVHAIASAGVA				
30		160	170	180	190	200
	NOV8	HAIKACASAGRMERCTCDEAFDLENREAWGCGGSEDIEFGGMVSRERAD				
	gi 15082261	HAIKACASAGRMERCTCDEAFDLENREAWGCGGDNLYSSKFVKERLG				
	gi 3915306	HAIKACASAGRMERCTCDEAFDLENREAWGCGGDNLYSNKFVKERLG				
	gi 16303264	HAIKACASAGRMERCTCDEAFDLENREAWGCGGDNLYSNKFVKERLG				
35	gi 7106447	FAVTRSCAEGSAAICCCSSRLQSGPGEWKGCGSEDIEFGGMVSRERAD				
	gi 5821261	FAVTRSCAEGSATICCCDTRHKGSPGEWKGCGSEDIEFGGMVSRERAD				
40		210	220	230	240	250
	NOV8	ARENRPDARSAMNRRHNNEAGROVIKAGVETTCCKCHGVSGSCTVRTCWRQL				
	gi 15082261	RRSEK-DLRARVDFHNNLVGVYVIKAGVETTCCKCHGVSGSCTVRTCWRQL				
	gi 3915306	RKPNK-DLRARVDFHNNLVGVYVIKAGVETTCCKCHGVSGSCTVRTCWRQL				
	gi 16303264	SKRNKDLRARDAHNTHVCIKAVKSGURTTCCKCHGVSGSCTVRTCWRQL				
45	gi 7106447	ARENRPDARSAMNRRHNNEAGROATASHHLKCKCHGVSGSCTVRTCWRQL				
	gi 5821261	ARENRPDARSAMNRRHNNEAGRTSILEHLKCKCHGVSGSCTVRTCWRQL				
50		260	270	280	290	300
	NOV8	APPHEVGKHLKHYESALKVGSITNEAAGEAGAIAPPGRASGAGGSDPY				
	gi 15082261	APPHEVGKHLKHYETALKVGSITNEAAGEAGAIAPPGRASGAGGSDPY				
	gi 3915306	SPFHEIGKQLKQYETSLKVGSTNEATGE-GDISPPK--KSI PGHSDQI				
	gi 16303264	SPFHEIGKQLKQYETSLKVGSTNEATGE-GDISPPK--KSI PGHSDQI				
	gi 7106447	PDERTIGDFLKQYDSASEMVVEKRESRGWVETLRPR--Y---TYFKY				
	gi 5821261	PDERTIGDFLKQYDSASEMVVEKRESRGWVETLRPR--Y---NFFKA				
55		310	320	330	340	350
	NOV8	PRTPBLVHDDSPSFCLAG--RSPGTACRRCHREKN---CESICCGRG				
	gi 15082261	PRTPBLVHDDSPSFCLAG--RSPGTACRRCHREKN---CESICCGRG				
	gi 3915306	PRTPBLVHDDSPSFCLAG--RSPGTACRRCHREKN---CESICCGRG				
60	gi 16303264	PRTPBLVHDDSPSFCLAG--RSPGTACRRCHREKN---CESICCGRG				
	gi 7106447	PRTPBLVHDDSPSFCLAG--RSPGTACRRCHREKN---CESICCGRG				
	gi 5821261	PRTPBLVHDDSPSFCLAG--RSPGTACRRCHREKN---CESICCGRG				
65		360	370	380		
	NOV8	HNTQSRVVTRPCCQVFWCCYVEORQCTQREBVYTCKG				
	gi 15082261	HNTQSRVVTRPCCQVFWCCYVEORQCTQREBVYTCKG				
	gi 3915306	HNTQSRVVTRPCCQVFWCCYVEORQCTQREBVYTCKG				
	gi 16303264	YDTQSRVLAFAFCHCOVFWCCYVEORQCTQREBVYTCKG				
70	gi 7106447	HNTQSRVVTRPCCQVFWCCYVEORQCTQREBVYTCKG				
	gi 5821261	HNTQSRVVTRPCCQVFWCCYVEORQCTQREBVYTCKG				

Tables 8E and 8F list the domain descriptions from DOMAIN analysis results against NOV8. This indicates that the NOV8 sequence has properties similar to those of other proteins known to contain this domain.

Table 8E. Domain Analysis of NOV8

gnl|Pfam|pfam00110, wnt, wnt family. (SEQ ID NO:104)
CD-Length = 313 residues, 99.7% aligned
Score = 313 bits (801), Expect = 1e-86

5	NOV 7:	48	CDRLK-LERKQRRMCRRDPGVAETLVEAVSMSALECQFQFRFERWNCTLEGRYRASL---	103
	Sbjct:	2	CRSLPGLSPRQRLCRRNPDMASVSEGAQLAIQECQHFRGRRWNCSTLDRLRVVFGKV	61
10	NOV 7:	104	LKRGFKETAFLYAISSAGLTHALAKACSAGRMERCTCDE-APDLENREGWKWGGCSEIDIE	162
	Sbjct:	62	LKKGTRETAFLVYAISSAGVAHAVTRACSEGELESCGCDYKKGPGGPQGSWQWGGCSDNVE	121
15	NOV 7:	163	FGGMVSREFADARENRPDARSAMNRHNEAGRQVIKAGVETTCCKHGVSGSCTVRTCWRQ	222
	Sbjct:	122	FGIRFSREFVDARERERDARSLMNLHNEAGRKAVKSHMRRECKCHGVSGSCSMKTCWLS	181
20	NOV 7:	223	LAPFHEVGKHLKHKYESALKV-GSTTNEAAGEAGAI SPPRGRASGAGGSDPLRTPPELVH	281
	Sbjct:	182	LPDFRAVGDAKDKYDGAIRVEPNKRGMGQSAPRLVAKNPRFKPPTRSD-----LVY	234
25	NOV 7:	282	LDDSPSFCL--AGRFSPGTAGRR-----HREKNCESICCGRGHNTQSRVVTRPCQCQVRW	335
	Sbjct:	235	LEDSPDYCERDRSTGSLGTQGRVCNKTSKGLDGCELLCCGRGYNTQQVERTEKCNCKFHW	294
	NOV 7:	336	CCYVECRQCTQREEVYTCK	354
	Sbjct:	295	CCYVKCEECQEVVEVHTCK	313

Table 8F. Domain Analysis of NOV8

gnl|Smart|smart00097, WNT1, found in Wnt-1 (SEQ ID NO:105)
CD-Length = 304 residues, 98.7% aligned
Score = 292 bits (748), Expect = 2e-80

30	NOV 7:	53	LERKQRRMCRRDPGVAETLVEAVSMSALECQFQFRFERWNCTLEGRYRA--SLLKRGFKE	110
	Sbjct:	5	LSRRRQRLCRANPDVMAVAEGAQEGIEECQHFRFRRWNCSTAGLASIFGKVLRRQGTRE	64
35	NOV 7:	111	TAFLYAISSAGLTHALAKACSAGRMERCTCDEAPDLENREGWKWGGCSEIDIEFGGMVSRE	170
	Sbjct:	65	TAFVYAISSAGVAHAVTRACSEGELESCGCDYSKRGSGGRGWEGGCSNDIDFGIGFSRE	124
40	NOV 7:	171	FADARENRPDARSAMNRHNEAGRQVIKAGVETTCCKHGVSGSCTVRTCWRQLAPFHEV	229
	Sbjct:	125	FVDARERRGSDARALMNLHNEAGRLAVKKTMKRECKCHGVSGSCSVKTCWLQLEPFREI	184
45	NOV 7:	230	GKHLKHKYESALKVGGSTTNEAAGEAGAI SPPRGRASGAGGSDPLRTPPELVHLLDDSPSFC	289
	Sbjct:	185	GDYLKEKYDGA SEVLD-----KRGTRGLVPANRDFKPTNTDLVYLESSPDFC	233
	NOV 7:	290	LAGRF--SPGTAGRRCHREKN-----CESICCGRGHNTQSRVVTRPCQCQVRWCCYVECRQ	343

Sbjct: 234 EKNPKTGSLGTQGRVCNKTSKGLDGCDDLCCGRGYNTEHVEVVERCNCCKFWCCYVKCKQ 293
 NOV 7: 344 CTQREEVYTCK 354
 | + | | + | | |
 5 Sbjct: 294 CRERVEKHTCK 304

Wnt proteins constitute a large family of molecules involved in cell proliferation, cell differentiation and embryonic patterning. They are known to interact with the Frizzled family of receptors to activate two main intracellular signaling pathways regulating intracellular calcium levels and gene transcription. Early studies on Wnts implicated them in cell proliferation and tumorigenesis, which have been borne out by recent work using transgenic and null mutant mice. Wnts are involved in processes involved in mammary gland development and cancer. Recent studies have demonstrated that these molecules are critical to organogenesis of several systems, such as the kidney and brain. Wnts regulate the early development, i.e. neural induction, and their role persists in later stages of development as well as in the mature organ. An example of this is seen in the brain, where the loss of certain Wnts leads to the absence of critical regions of the brain, e.g. the hippocampus, involved in learning and memory, or the cerebellum, involved in motor function. Wnts have also been implicated in the genesis of degenerative diseases such as Alzheimer's disease. The protein encoded by the novel gene described herein may therefore play a role in cellular proliferation, differentiation, dysregulation, organogenesis and disease processes such as cancer, developmental defects etc.

Alzheimer's disease (AD) is a neurodegenerative disease with progressive dementia accompanied by three main structural changes in the brain: diffuse loss of neurons; intracellular protein deposits termed neurofibrillary tangles (NFT) and extracellular protein deposits termed amyloid or senile plaques, surrounded by dystrophic neurites. Two major hypotheses have been proposed in order to explain the molecular hallmarks of the disease: The 'amyloid cascade' hypothesis and the 'neuronal cytoskeletal degeneration' hypothesis. While the former is supported by genetic studies of the early-onset familial forms of AD (FAD), the latter revolves around the observation in vivo that cytoskeletal changes - including the abnormal phosphorylation state of the microtubule associated protein tau - may precede the deposition of senile plaques. Recent studies have suggested that the trafficking process of membrane associated proteins is modulated by the FAD-linked presenilin (PS) proteins, and that amyloid beta-peptide deposition may be initiated intracellularly, through the secretory pathway. Current hypotheses concerning presenilin function are based upon its cellular localization and its putative interaction as macromolecular complexes with the cell-adhesion/signaling beta-catenin molecule and the glycogen synthase kinase 3beta (GSK-3beta)

enzyme. Developmental studies have shown that PS proteins function as components in the Notch signal transduction cascade and that beta-catenin and GSK-3beta are transducers of the Wnt signaling pathway. Both pathways are thought to have an important role in brain development, and they have been connected through Dishevelled (Dvl) protein, a known
5 transducer of the Wnt pathway.

Members of the vertebrate Wnt family have been subdivided into two functional classes according to their biological activities. Some Wnts signal through the canonical Wnt-1/wingless pathway by stabilizing cytoplasmic beta-catenin. By contrast other Wnts stimulate intracellular Ca²⁺ release and activate two kinases, CamKII and PKC, in a G-protein-
10 dependent manner. Moreover, putative Wnt receptors belonging to the Frizzled gene family have been identified that preferentially couple to the two prospective pathways in the absence of ectopic Wnt ligand and that might account for the signaling specificity of the Wnt pathways. As Ca²⁺ release was the first described feature of the noncanonical pathway, and as Ca²⁺ probably plays a key role in the activation of CamKII and PKC, Kuhl M, et al., (*Trends*
15 *Genet* 2000 Jul;16(7):279-83) have named this Wnt pathway the Wnt/Ca²⁺ pathway.

Many constituents of Wnt signaling pathways are expressed in the developing and mature nervous systems. Recent work has shown that Wnt signaling controls initial formation of the neural plate and many subsequent patterning decisions in the embryonic nervous system, including formation of the neural crest. Wnt signaling continues to be important at
20 later stages of development. Wnts have been shown to regulate the anatomy of the neuronal cytoskeleton and the differentiation of synapses in the cerebellum. Wnt signaling has been demonstrated to regulate apoptosis and may participate in degenerative processes leading to cell death in the aging brain.

Recent genetic studies have shown that the signalling factor Wnt3a is required for
25 formation of the hippocampus; the developmental consequences of Wnt signalling in the hippocampus are mediated by multiple HMG-box transcription factors, with LEF-1 being required just for formation of the dentate gyrus.

Wnt-1 was first identified as a protooncogene activated by viral insertion in mouse mammary tumors. Transgenic expression of this gene using a mouse mammary tumor virus
30 LTR enhancer causes extensive ductal hyperplasia early in life and mammary adenocarcinomas in approximately 50% of the female transgenic (TG) mice by 6 months of age. Metastasis to the lung and proximal lymph nodes is rare at the time tumors are detected but frequent after the removal of the primary neoplasm. The potent mitogenic effect mediated by Wnt-1 expression does not require estrogen stimulation; tumors form after an increased

latency in estrogen receptor alpha-null mice. Several genetic lesions, including inactivation of p53 and over-expression of Fgf-3, collaborate with Wnt-1 in leading to mammary tumors, but loss of Sky and inactivation of one allele of Rb do not affect the rate of tumor formation in Wnt-1 TG mice.

5 Communication between cells is often mediated by secreted signaling molecules that bind cell surface receptors and modulate the activity of specific intracellular effectors. The Wnt family of secreted glycoproteins is one group of signaling molecules that has been shown to control a variety of developmental processes including cell fate specification, cell proliferation, cell polarity and cell migration. In addition, mis-regulation of Wnt signaling can
10 cause developmental defects and is implicated in the genesis of several human cancers. The importance of Wnt signaling in development and in clinical pathologies is underscored by the large number of primary research papers examining various aspects of Wnt signaling that have been published in the past several years.

 Reproductive tract development and function is regulated by circulating steroid
15 hormones. In the mammalian female reproductive tract, estrogenic compounds direct many aspects of cytodifferentiation including uterine gland formation, smooth muscle morphology, and epithelial differentiation. While it is clear that these hormones act through their cognate nuclear receptors, it is less clear what signaling events follow hormonal stimulation that govern cytodifferentiation. Recent advances in molecular embryology and cancer cell biology
20 have identified the Wnt family of secreted signaling molecules. Discussed here are recent advances that point to a definitive role during uterine development and adult function for one member of the Wnt gene family, Wnt-7a. In addition, recent data is reviewed that implicates Wnt-7a deregulation in response to pre-natal exposure to the synthetic estrogenic compound, DES. These advances point to an important role for the Wnt gene family in various
25 reproductive tract pathologies including cancer.

 Holoprosencephaly (HPE) is the most common developmental defect of the forebrain in humans. Several distinct human genes for holoprosencephaly have now been identified. They include Sonic hedgehog (SHH), ZIC2, and SIX3. Many additional genes involved in forebrain development are rapidly being cloned and characterized in model vertebrate
30 organisms. These include Patched (Ptc), Smoothened (Smo), cubitus interruptus (ci)/Gli, wingless (wg)/Wnt, decapentaplegic (dpp)/BMP, Hedgehog interacting protein (Hip), nodal, Smads, One-eyed pinhead (Oep), and TG-Interacting Factor (TGIF). However, further analysis is needed before their roles in HPE can be established.

Female reproductive hormones control mammary gland morphogenesis. In the absence of the progesterone receptor (PR) from the mammary epithelium, ductal side-branching fails to occur. Briskin C, et al. (*Genes Dev* 2000 Mar 15;14(6):650-4) overcame this defect by ectopic expression of the protooncogene Wnt-1. Transplantation of mammary epithelia from Wnt-4(-) 5)/(-) mice shows that Wnt-4 has an essential role in side-branching early in pregnancy. PR and Wnt-4 mRNAs colocalize to the luminal compartment of the ductal epithelium. Progesterone induces Wnt-4 in mammary epithelial cells and is required for increased Wnt-4 expression during pregnancy. Thus, Wnt signaling is essential in mediating progesterone function during mammary gland morphogenesis.

10 Synapse formation requires changes in cell morphology and the upregulation and localization of synaptic proteins. In the cerebellum, mossy fibers undergo extensive remodeling as they contact several granule cells and form complex, multisynaptic glomerular rosettes. Hall AC, et al., (*Cell* 2000 Mar 3;100(5):525-35) showed that granule cells secrete factors that induce axon and growth cone remodeling in mossy fibers. This effect is blocked by the 15 WNT antagonist, sFRP-1, and mimicked by WNT-7a, which is expressed by granule cells. WNT-7a also induces synapsin I clustering at remodeled areas of mossy fibers, a preliminary step in synaptogenesis. Wnt-7a mutant mice show a delay in the morphological maturation of glomerular rosettes and in the accumulation of synapsin I. We propose that WNT-7a can function as a synaptogenic factor.

20 Estrogens have important functions in mammary gland development and carcinogenesis. To better define these roles, Bocchinfuso WP, et al., (*Cancer Res* 1999 Apr 15;59(8):1869-76) have used two previously characterized lines of genetically altered mice: estrogen receptor-alpha (ER alpha) knockout (ERKO) mice, which lack the gene encoding ER alpha, and mouse mammary virus tumor (MMTV)-Wnt-1 transgenic mice (Wnt-1 TG), which 25 develop mammary hyperplasia and neoplasia due to ectopic production of the Wnt-1 secretory glycoprotein. Bocchinfuso WP, et al. have crossed these lines to ascertain the effects of ER alpha deficiency on mammary gland development and carcinogenesis in mice expressing the Wnt-1 transgene. Introduction of the Wnt-1 transgene into the ERKO background stimulates proliferation of alveolar-like epithelium, indicating that Wnt-1 protein can promote 30 mitogenesis in the absence of an ER alpha-mediated response. The hyperplastic glandular tissue remains confined to the nipple region, implying that the requirement for ER alpha in ductal expansion is not overcome by ectopic Wnt-1. Tumors were detected in virgin ERKO females expressing the Wnt-1 transgene at an average age (48 weeks) that is twice that seen in virgin Wnt-1 TG mice (24 weeks) competent to produce ER alpha. Prepubertal ovariectomy of

Wnt-1 TG mice also extended tumor latency to 42 weeks. However, pregnancy did not appear to accelerate the appearance of tumors in Wnt-1 TG mice, and tumor growth rates were not measurably affected by late ovariectomy. Small hyperplastic mammary glands were observed in Wnt-1 TG males, regardless of ER alpha gene status; the glands were similar in appearance to those found in ERKO/Wnt-1 TG females. Mammary tumors also occurred in Wnt-1 TG males; latency tended to be longer in the heterozygous ER alpha and ERKO males (86 to 100 weeks) than in wild-type ER alpha mice (ca. 75 weeks). Bocchinfuso WP, et al. concluded that ectopic expression of the Wnt-1 proto-oncogene can induce mammary hyperplasia and tumorigenesis in the absence of ER alpha in female and male mice. The delayed time of tumor appearance may depend on the number of cells at risk of secondary events in the hyperplastic glands, on the carcinogenesis-promoting effects of ER alpha signaling, or on both.

Wnt-1 and Wnt-3a proto-oncogenes have been implicated in the development of midbrain and hindbrain structures. Evidence for such a role has been derived from in situ hybridization studies showing Wnt-1 and -3a expression in developing cranial and spinal cord regions and from studies of mutant mice whose Wnt-1 genes have undergone targeted disruption by homologous recombination. Wnt-1 null mutants exhibit cranial defects but no spinal cord abnormalities, despite expression of the gene in these regions. The absence of spinal cord abnormalities is thought to be due to a functional compensation of the Wnt-1 deficiency by related genes, a problem that has complicated the analysis of null mutants of other developmental genes as well. Augustine K, et al., (*Dev Genet* 1993;14(6):500-20) describe the attenuation of Wnt-1 expression using antisense oligonucleotide inhibition in mouse embryos grown in culture. Augustine K, et al. induced similar mid- and hindbrain abnormalities as those seen in the Wnt-1 null mutant mice. Attenuation of Wnt-1 expression was also associated with cardiomegaly resulting in hemostasis. These findings are consistent with the possibility that a subset of Wnt-1 expressing cells include neural crest cells known to contribute to septation of the truncus arteriosus and to formation of the visceral arches. Antisense knockout of Wnt-3a, a gene structurally related to Wnt-1, targeted the forebrain and midbrain region, which were hypoplastic and failed to expand, and the spinal cord, which exhibited lateral outpocketings at the level of the forelimb buds. Dual antisense knockouts of Wnt-1 and Wnt-3a targeted all brain regions leading to incomplete closure of the cranial neural folds, and an increase in the number and severity of outpocketings along the spinal cord, suggesting that these genes complement one another to produce normal patterning of the spinal cord. The short time required to assess the mutant phenotype (2 days) and the need for limited sequence information of the target gene (20-25 nucleotides) make this antisense

oligonucleotide/whole embryo culture system ideal for testing the importance of specific genes and their interactions in murine embryonic development.

Wnt-1 (previously known as int-1) is a proto-oncogene induced by the integration of the mouse mammary tumor virus. It is thought to play a role in intercellular communication and seems to be a signalling molecule important in the development of the central nervous system (CNS). The sequence of wnt-1 is highly conserved in mammals, fish, and amphibians. Wnt-1 is a member of a large family of related proteins that are all thought to be developmental regulators. These proteins are known as wnt-2 (also known as irp), wnt-3 up to wnt-15. At least four members of this family are present in *Drosophila*. One of them, wingless (wg), is implicated in segmentation polarity. All these proteins share the following features characteristics of secretory proteins, a signal peptide, several potential N-glycosylation sites and 22 conserved cysteines that are probably involved in disulfide bonds. The Wnt proteins seem to adhere to the plasma membrane of the secreting cells and are therefore likely to signal over only few cell diameters.

The disclosed NOV8 nucleic acid of the invention encoding a Wnt-14-like protein includes the nucleic acid whose sequence is provided in Table 8A or a fragment thereof. The invention also includes a mutant or variant nucleic acid any of whose bases may be changed from the corresponding base shown in Table 8A while still encoding a protein that maintains its Wnt-14-like activities and physiological functions, or a fragment of such a nucleic acid. The invention further includes nucleic acids whose sequences are complementary to those just described, including nucleic acid fragments that are complementary to any of the nucleic acids just described. The invention additionally includes nucleic acids or nucleic acid fragments, or complements thereto, whose structures include chemical modifications. Such modifications include, by way of nonlimiting example, modified bases, and nucleic acids whose sugar phosphate backbones are modified or derivatized. These modifications are carried out at least in part to enhance the chemical stability of the modified nucleic acid, such that they may be used, for example, as antisense binding nucleic acids in therapeutic applications in a subject. In the mutant or variant nucleic acids, and their complements, up to about 23 percent of the bases may be so changed.

The disclosed NOV8 protein of the invention includes the Wnt-14-like protein whose sequence is provided in Table 8B. The invention also includes a mutant or variant protein any of whose residues may be changed from the corresponding residue shown in Table 8B while still encoding a protein that maintains its Wnt-14-like activities and physiological functions, or

a functional fragment thereof. In the mutant or variant protein, up to about 24 percent of the residues may be so changed.

The protein similarity information, expression pattern, and map location for the Wnt-14-like protein and nucleic acid (NOV8) disclosed herein suggest that NOV8 may have
 5 important structural and/or physiological functions characteristic of the Wnt-14-like family. Therefore, the NOV8 nucleic acids and proteins of the invention are useful in potential diagnostic and therapeutic applications. These include serving as a specific or selective nucleic acid or protein diagnostic and/or prognostic marker, wherein the presence or amount of the nucleic acid or the protein are to be assessed, as well as potential therapeutic
 10 applications such as the following: (i) a protein therapeutic, (ii) a small molecule drug target, (iii) an antibody target (therapeutic, diagnostic, drug targeting/cytotoxic antibody), (iv) a nucleic acid useful in gene therapy (gene delivery/gene ablation), and (v) a composition promoting tissue regeneration in vitro and in vivo.

The NOV8 nucleic acids and proteins of the invention are useful in potential diagnostic
 15 and therapeutic applications implicated in various diseases and disorders described below and/or other pathologies. For example, the compositions of the present invention will have efficacy for treatment of patients suffering from Von Hippel-Lindau (VHL) syndrome , Alzheimer's disease, stroke, tuberous sclerosis, hypercalceimia, Parkinson's disease, Huntington's disease, cerebral palsy, epilepsy, Lesch-Nyhan syndrome, multiple sclerosis,
 20 ataxia-telangiectasia, leukodystrophies, behavioral disorders, addiction, anxiety, pain, neurodegeneration, cancer, developmental defects, and/or other pathologies/disorders. The NOV8 nucleic acid, or fragments thereof, may further be useful in diagnostic applications, wherein the presence or amount of the nucleic acid or the protein are to be assessed.

NOV8 nucleic acids and polypeptides are further useful in the generation of antibodies
 25 that bind immunospecifically to the novel substances of the invention for use in therapeutic or diagnostic methods. These antibodies may be generated according to methods known in the art, using prediction from hydrophobicity charts, as described in the "Anti-NOVX Antibodies" section below. For example the disclosed NOV8 protein have multiple hydrophilic regions, each of which can be used as an immunogen. In one embodiment, contemplated NOV8
 30 epitope is from about amino acids 40 to 70. In another embodiment, the contemplated NOV8 epitope is from about amino acids 80 to 110. In further embodiments, the contemplated NOV8 epitope is from about amino acids 120 to 200, from about amino acids 220 to 245, from about amino acids 250 to 280, or from about amino acids 290 to 340. This novel protein also has value in development of powerful assay system for functional analysis of various human

disorders, which will help in understanding of pathology of the disease and development of new drug targets for various disorders.

NOV9

- 5 A disclosed NOV9 nucleic acid of 2037 nucleotides (also referred to as AC069250_28_da1) encoding a beta-adrenergic receptor kinase-like protein is shown in Table 9A. An open reading frame was identified beginning with an ATG initiation codon at nucleotides 16-18 and ending with a TGA codon at nucleotides 2020-2022. A putative untranslated region upstream from the initiation codon and downstream from the termination
- 10 codon is underlined in Table 9A. The start and stop codons are in bold letters. Single nucleotide polymorphism data for NOV9 is discussed in further detail in Example 3.

Table 9A. NOV9 nucleotide sequence (SEQ ID NO:23).

GCCGCCGCCCAAGATGGCGGACCTGGAGGCGGTGCTGGCCGACGTGAGCTACCTGATGGCCATGGAGAAG
AGCAAGGCCACGCCGCCGCCGCCGCCAGCAAGAAGATACTGCTGCCCGAGCCAGCATCCGCGAGTGTATG
CAGAAGTACCTGGAGGACCGGGCGAGGTGACCTTTGAGAAGATCTTTTCCAGAAAGCTGGGGTACCTGCTC
TTCCGAGACTTCTGCCTGAACCACCTGGAGGAGGCCAGGCCCTTGGTGGAAATCTATGAGGAGATCAAGAAG
TACGAGAAGCTGGAGACGGAGGAGGAGCGTGTGGCCCCGACGCCGGGAGATCTTCGACTCATACATCATGAAG
GAGCTGCTGGCCTGCTCGCATCCCTTCTCGAAGAGTGCCACTGAGCATGTCCAAGGCCACCTGGGGAAGAAG
CAGGTGCCTCCGGATCTCTCCAGCCATACATCGAAGAGATTTGTCAAAACCTCCGAGGGGACGTGTTCCAG
AAATTCAATTGAGAGCGATAAGTTACACGGTTTTGCCAGTGGAAGAATGTGGAGCTCAACATCCACCTGACC
ATGAATGACTTCAGCGTGCATCGCATCATTGGGCGCGGGGCTTGGCGAGGTCTATGGGTGCCGAAGGCT
GACACAGGCAAGATGTACGCCATGAAGTGCTGGACAAAAAGCGCATCAAGATGAAGCAGGGGAGACCCTG
GCCCTGAACGAGCGCATATGCTCTCGCTCGTCAGCACTGGGGACTGCCCATTCATTGTCTGCATGTATAC
GCGTTCCACACGCCAGACAAGCTCAGCTTCATCCTGGACCTCATGAACGGTGGGGACCTGCACCTACCACTC
TCCCAGCACGGGGTCTTCTCAGAGGCTGACATGCGCTTCTATGCGGCCGAGATCATCCTGGGCTGGAGCAC
ATGCACAAACCGCTTCGTGGTCTACCGGGACCTGAAGCCAGCCAAACATCCTTCTGGACGAGCATGGCCACGTG
CGGATCTCGGACCTGGGCTGGCCTGTGACTTCTCAAGAAGAAGCCCCATGCCAGCGTGGGCAACCCACGGG
TACATGGCTCCGAGGTCTGTCAGAAGGGCGTGGCCTACGACAGCAGTGCCGACTGGTTCTCTCTGGGGTGC
ATGCTCTTCAAGTTGCTGCGGGGGCACAGCCCTTCCGGCAGCACAAAGACAAAGACAAGCATGAGATCGAC
CGCATGACGCTGACGATGGCCGTGGAGCTGCCCGACTCCTTCTCCCTGAACTACGCTCCCTGCTGGAGGGG
TTGCTGCAGAGGGATGTCAACCGGAGATTGGGCTGCCTGGGCCGAGGGGCTCAGGAGGTGAAAGAGAGCCCC
TTTTCCGCTCCCTGGACTGGCAGATGGTCTTCTTGAGAAAGTACCTCCCGGCTGATCCCCCAGAGGG
GAGGTGAACGCGGCCGACGCCTTCGACATTGGCTCCTTCGATGAGGAGGACAAAAAGGAATCAAGCAGGAG
GTGGCAGAGACTGTCTTCGACACCATCAACGCTGAGACAGACCGGCTGGAGGCTCGCAAGAAGCCAAAGAAC
AAGCAGCTGGGCCATGAGGAAGACTACGCCCTGGGCAAGGACTGCATCATGCTATGCTACATGTCCAAAGATG
GGCAACCCCTTCTGACCCAGTGGCAGCGGGGCTACTTCTACCTGTTCCCCAACCGCTCGAGTGGCGGGG
GAGGGCGAGGCCCGCAGAGCCTGCTGACCATGGAGGAGATCCAGTCGGTGGAGGAGACGCAGATCAAGGAG
CGCAAGTGCCCTGCTCCTCAAGATCCGCGGTGGGAAACAGTTTCAATTTGCAAGTGCATAGCGACCCTGAGCTG
GTGCAAGTGAAGAAGGAGCTGCGCGACGCCCTACCGCGAGGCCAGCAGCTGGTGCAGCGGGTCCCCAAGATG
AAGAACAAGCCGCTCGCCCGTGGTGGAGCTGAGCAAGGTGCCGCTGGTCCAGCGGGCAGTGCCAAACGGC
CTCTGACCCGCCACCCGCT

- 15 In a search of public sequence databases, the NOV9 nucleic acid sequence, located on chromosome 11 has 1546 of 1574 bases (98%) identical to a beta-adrenergic receptor kinase 1 mRNA from *Homo sapiens*, (GENBANK-ID: HUMBARK1A) (E = 0.0). Public nucleotide databases include all GenBank databases and the GeneSeq patent database.

The disclosed NOV9 polypeptide (SEQ ID NO:24) encoded by SEQ ID NO:23 has 668 amino acid residues and is presented in Table 9B using the one-letter amino acid code. Signal P, Psort and/or Hydropathy results predict that NOV9 has no signal peptide and is likely to be localized in the nucleus with a certainty of 0.3000. In other embodiments, NOV9 may also be localized to the microbody (peroxisome) with a certainty of 0.1478, the mitochondrial matrix (lumen) with a certainty of 0.1000 or in the lysosome (lumen) with a certainty of 0.1000.

Table 9B. Encoded NOV9 protein sequence (SEQ ID NO:24).
MADLEAVLADVSYLMAMEKSKATPAARASKKILLPEPSIRSVMQKYLEDRGEVTFEKIFSQKLGYLLFRDFC LNHLEEARPLVEFYEEIKKYEKLETEEERVARSRIFDSYIMKELLACSHPFSSKATEHVQGHGKQVPPD LFQPYIEEICQNLRGDVFQKFIESDKFTRFCQWKNVELNIHLTMNDFSVHRIIGRGGFGEVYGCRKADTGKM YAMKCLDKKRIKMKOGETLALNERIMLSLVSTGDCPFIVCMSYAFHTPKLSFILDLMNGGDLHYHLSQHGV PSEADMRFYAAEILGLEHMHNRFFVYRDLKPANILLDEHGHVIRISDLGLACDFSKKKPHASVGTGHYMAPE VLQKGVAIDSSADWFSLGCMLFKLLRGHSPFRQHKTKDKHEIDRMTLTMAVELPDSFSPELRSLLLEGLLQRD VNRRLGCLGRGAQEVKESPFERSLDWQMVFLQKYPPLIPPRGEVNAADAFDIGSFDEEDTKGIKQVEAETV FDTINAETDRLEARKKAKNKQLGHEEDYALGKDCIMHGYMSKMGNPFLTQWQRRYFYLFPNRLWRGEGEAP QSLLTMEETQSVEETQIKERKCLLLKIRGGKQFILQCSDPELVQWKKELRDYREAQQLVQRVPMKNKPR SPVVELSKVPLVQRGSANGL

A search of sequence databases reveals that the NOV9 amino acid sequence has 495 of 497 amino acid residues (99%) identical to, and 495 of 497 amino acid residues (99%) similar to, the 689 amino acid residue beta-adrenergic receptor kinase from *Homo sapiens* (A53791) (E = 0.0). Public amino acid databases include the GenBank databases, SwissProt, PDB and PIR.

NOV9 is expressed in at least the following tissues: adrenal gland, bone marrow, brain - amygdala, brain - cerebellum, brain - hippocampus, brain - substantia nigra, brain - thalamus, brain - whole, fetal brain, fetal kidney, fetal liver, fetal lung, heart, kidney, lymphoma - Raji, mammary gland, pancreas, pituitary gland, placenta, prostate, salivary gland, skeletal muscle, small intestine, spinal cord, spleen, stomach, testis, thyroid, trachea, uterus. This information was derived by determining the tissue sources of the sequences that were included in the invention including but not limited to SeqCalling sources, Public EST sources, Literature sources, and/or RACE sources.

In addition, the sequence is predicted to be expressed in blood leukocytes because of the expression pattern of (GENBANK-ID:gb:GENBANK-ID:HUMBARK1A|acc:M80776.1) a closely related Human beta-adrenergic receptor kinase 1 mRNA, complete cds homolog in species *Homo sapiens*.

The disclosed NOV9 polypeptide has homology to the amino acid sequences shown in the BLASTP data listed in Table 9C.

Table 9C. BLAST results for NOV9					
Gene Index/ Identifier	Protein/ Organism	Length (aa)	Identity (%)	Positives (%)	Expect
ptnr:pir-id:A53791	beta-adrenergic-receptor kinase (EC 2.7.1.126) 1 - human	689	495/497 (99%)	495/497 (99%)	0.0
ptnr:SWISSPROT- ACC:P25098	Beta-adrenergic receptor kinase 1 (EC 2.7.1.126)	689	494/497 (99%)	495/497 (99%)	0.0
ptnr:SPTREMBL- ACC:Q99LL8	SIMILAR TO ADRENERGIC, BETA, RECEPTOR KINASE 1 - Mus musculus	687	490/495 (98%)	493/495 (99%)	0.0
ptnr:SWISSPROT- ACC:P26817	Beta-adrenergic receptor kinase 1	689	489/497 (98%)	493/497 (99%)	0.0
ptnr:SPTREMBL- ACC:Q99MK8	G PROTEIN RECEPTOR KINASE 2	689	490/497 (98%)	494/497 (99%)	0.0

- 5 The homology between these and other sequences is shown graphically in the ClustalW analysis shown in Table 9D. In the ClustalW alignment of the NOV9 proteins, as well as all other ClustalW analyses herein, the black outlined amino acid residues indicate regions of conserved sequence (*i.e.*, regions that may be required to preserve structural or functional properties), whereas non-highlighted amino acid residues are less conserved and
- 10 can potentially be altered to a much broader extent without altering protein structure or function.

Table 9D. ClustalW Analysis of NOV9

- 15 1) NOV9 (SEQ ID NO:24)
2) ptnr:pir-id:A53791 beta-adrenergic-receptor kinase (EC 2.7.1.126) 1 (SEQ ID NO:69)
3) ptnr:SWISSPROT-ACC:P25098 Beta-adrenergic receptor kinase 1 (EC 2.7.1.126) (SEQ ID NO:70)
20 4) ptnr:SPTREMBL-ACC:Q99LL8 SIMILAR TO ADRENERGIC, BETA, RECEPTOR KINASE 1 - Mus musculus (Mouse) (SEQ ID NO:71)
5) 6) ptnr:SWISSPROT-ACC:P26817 Beta-adrenergic receptor kinase 1 (EC 2.7.1.126) (Beta-ARK-1) (SEQ ID NO:72)
- 25 NOV9 MADLEAVLADVSYLMAMEKSKATPAARASKKILLPEPSIRSVMQKYLEDRGEVTFEKIFS 60
A53791 MADLEAVLADVSYLMAMEKSKATPAARASKKILLPEPSIRSVMQKYLEDRGEVTFEKIFS 60
P25098 MADLEAVLADVSYLMAMEKSKATPAARASKKILLPEPSIRSVMQKYLEDRGEVTFEKIFS 60
Q99LL8 --DLEAVLADVSYLMAMEKSKATPAARASKKILLPEPSIRSVMQKYLEDRGEVTFEKIFS 58
P26817 MADLEAVLADVSYLMAMEKSKATPAARASKKILLPEPSIRSVMQKYLEDRGEVTFEKIFS 60
- 30 NOV9 QKLGYYLLFRDFCLNHLEEARPLVEFYEEIKKYEKLETEEERVARSR EIFDSYIMKELLAC 120
A53791 QKLGYYLLFRDFCLNHLEEARPLVEFYEEIKKYEKLETEEERVARSR EIFDSYIMKELLAC 120

	P25098	QKLGYLLFRDFCLNHLEEARPLVEFYEEIKKYEKLETEEBERVRSREIFDSYIMKELLAC	120
	Q99LL8	QKLGYLLFRDFCLNHLEEARPLVEFYEEIKKYEKLETEEBERVRSREIFDSYIMKELLAC	118
	P26817	QKLGYLLFRDFCLNHLEEARPLVEFYEEIKKYEKLETEEBERVRSREIFDSYIMKELLAC	120
5	NOV9	SHPFKSASATEHVQGHGKQVPPDLFPQYIEEIQCNLRGDVFQKFIESDKFTRFCQWKNV	180
	A53791	SHPFKSASATEHVQGHGKQVPPDLFPQYIEEIQCNLRGDVFQKFIESDKFTRFCQWKNV	180
	P25098	SHPFKSASATEHVQGHGKQVPPDLFPQYIEEIQCNLRGDVFQKFIESDKFTRFCQWKNV	180
	Q99LL8	SHPFKSASATEHVQGHGKQVPPDLFPQYIEEIQCNLRGDVFQKFIESDKFTRFCQWKNV	178
	P26817	SHPFKSASATEHVQGHGKQVPPDLFPQYIEEIQCNLRGDVFQKFIESDKFTRFCQWKNV	180
10	NOV9	ELNIHLTMNDFSVMHRIIGRGGFGEVYGCRAKDTGKMYAMKCLDKKRIKMKQGETLALNER	240
	A53791	ELNIHLTMNDFSVMHRIIGRGGFGEVYGCRAKDTGKMYAMKCLDKKRIKMKQGETLALNER	240
	P25098	ELNIHLTMNDFSVMHRIIGRGGFGEVYGCRAKDTGKMYAMKCLDKKRIKMKQGETLALNER	240
	Q99LL8	ELNIHLTMNDFSVMHRIIGRGGFGEVYGCRAKDTGKMYAMKCLDKKRIKMKQGETLALNER	238
	P26817	ELNIHLTMNDFSVMHRIIGRGGFGEVYGCRAKDTGKMYAMKCLDKKRIKMKQGETLALNER	240
15	NOV9	IMLSLVSTGDCPFIIVCMSYAFHTPDKLSFILDLMNGGDLHYHLSQHGVFSEADMRFYAAE	300
	A53791	IMLSLVSTGDCPFIIVCMSYAFHTPDKLSFILDLMNGGDLHYHLSQHGVFSEADMRFYAAE	300
	P25098	IMLSLVSTGDCPFIIVCMSYAFHTPDKLSFILDLMNGGDLHYHLSQHGVFSEADMRFYAAE	300
	Q99LL8	IMLSLVSTGDCPFIIVCMSYAFHTPDKLSFILDLMNGGDLHYHLSQHGVFSEADMRFYAAE	298
	P26817	IMLSLVSTGDCPFIIVCMSYAFHTPDKLSFILDLMNGGDLHYHLSQHGVFSEADMRFYAAE	300
20	NOV9	IILGLEHMHNRFFVYRDLKPAIILLDEHGHVRIIDLGLACDFSKKKPHASVGTGHCYMAPE	360
	A53791	IILGLEHMHNRFFVYRDLKPAIILLDEHGHVRIIDLGLACDFSKKKPHASVGTGHCYMAPE	360
	P25098	IILGLEHMHNRFFVYRDLKPAIILLDEHGHVRIIDLGLACDFSKKKPHASVGTGHCYMAPE	360
	Q99LL8	IILGLEHMHNRFFVYRDLKPAIILLDEHGHVRIIDLGLACDFSKKKPHASVGTGHCYMAPE	358
	P26817	IILGLEHMHNRFFVYRDLKPAIILLDEHGHVRIIDLGLACDFSKKKPHASVGTGHCYMAPE	360
25	NOV9	VLQKGVAYDSSADWFLGCMFLKLLRGHSPFRQHKTKDKHEIDRMTLTMAVELPDSFSPE	420
	A53791	VLQKGVAYDSSADWFLGCMFLKLLRGHSPFRQHKTKDKHEIDRMTLTMAVELPDSFSPE	420
	P25098	VLQKGVAYDSSADWFLGCMFLKLLRGHSPFRQHKTKDKHEIDRMTLTMAVELPDSFSPE	420
	Q99LL8	VLQKGVAYDSSADWFLGCMFLKLLRGHSPFRQHKTKDKHEIDRMTLTMAVELPDSFSPE	418
	P26817	VLQKGVAYDSSADWFLGCMFLKLLRGHSPFRQHKTKDKHEIDRMTLTMAVELPDSFSPE	420
30	NOV9	LRSLLGLELLQORDVNRRLGCLGRGAQEVKESPFRRSLDWQMVFLQKYPPLIPPRGEVNAA	480
	A53791	LRSLLGLELLQORDVNRRLGCLGRGAQEVKESPFRRSLDWQMVFLQKYPPLIPPRGEVNAA	480
	P25098	LRSLLGLELLQORDVNRRLGCLGRGAQEVKESPFRRSLDWQMVFLQKYPPLIPPRGEVNAA	480
	Q99LL8	LRSLLGLELLQORDVNRRLGCLGRGAQEVKESPFRRSLDWQMVFLQKYPPLIPPRGEVNAA	478
	P26817	LRSLLGLELLQORDVNRRLGCLGRGAQEVKESPFRRSLDWQMVFLQKYPPLIPPRGEVNAA	480
35	NOV9	DAFDIGSFDEEDTKGIK-----QEAETVFDITINAETDRLEARK	519
	A53791	DAFDIGSFDEEDTKGIKLLDSQELRYNFPPLTISERWQEQEAETVFDITINAETDRLEARK	540
	P25098	DAFDIGSFDEEDTKGIKLLDSQELRYNFPPLTISERWQEQEAETVFDITINAETDRLEARK	540
	Q99LL8	DAFDIGSFDEEDTKGIKLLDSQELRYNFPPLTISERWQEQEAETVFDITINAETDRLEARK	538
	P26817	DAFDIGSFDEEDTKGIKLLDSQELRYNFPPLTISERWQEQEAETVFDITINAETDRLEARK	540
40	NOV9	KAKNKQLGHEEDYALGKDCIMHGYMSKMGNPFLTQWQRRYFYLPNRLLEWRGEGEAPQSL	579
	A53791	KAKNKQLGHEEDYALGKDCIMHGYMSKMGNPFLTQWQRRYFYLPNRLLEWRGEGEAPQSL	600
	P25098	KAKNKQLGHEEDYALGKDCIMHGYMSKMGNPFLTQWQRRYFYLPNRLLEWRGEGEAPQSL	600
	Q99LL8	KAKNKQLGHEEDYALGKDCIMHGYMSKMGNPFLTQWQRRYFYLPNRLLEWRGEGEAPQSL	598
	P26817	KAKNKQLGHEEDYALGKDCIMHGYMSKMGNPFLTQWQRRYFYLPNRLLEWRGEGEAPQSL	600
50	NOV9	LTMBEIQSVEETQIKERKCLLLKIRGGKQFVLQCDSDPELVQWKKELRDAYREAQQLVQR	639
	A53791	LTMBEIQSVEETQIKERKCLLLKIRGGKQFVLQCDSDPELVQWKKELRDAYREAQQLVQR	660
	P25098	LTMBEIQSVEETQIKERKCLLLKIRGGKQFVLQCDSDPELVQWKKELRDAYREAQQLVQR	660
	Q99LL8	LTMBEIQSVEETQIKERKCLLLKIRGGKQFVLQCDSDPELVQWKKELRDAYREAQQLVQR	658
	P26817	LTMBEIQSVEETQIKERKCLLLKIRGGKQFVLQCDSDPELVQWKKELRDAYREAQQLVQR	660
55	NOV9	VPKMKNKPRSPVVVELSKVPLVQRGSANGL	668
	A53791	VPKMKNKPRSPVVVELSKVPLVQRGSANGL	689
	P25098	VPKMKNKPRSPVVVELSKVPLVQRGSANGL	689
	Q99LL8	VPKMKNKPRSPVVVELSKVPLVQRGSANGL	687
	P26817	VPKMKNKPRSPVVVELSKVPLVQRGSANGL	689
60	NOV9	VPKMKNKPRSPVVVELSKVPLVQRGSANGL	668
	A53791	VPKMKNKPRSPVVVELSKVPLVQRGSANGL	689
	P25098	VPKMKNKPRSPVVVELSKVPLVQRGSANGL	689
	Q99LL8	VPKMKNKPRSPVVVELSKVPLVQRGSANGL	687
	P26817	VPKMKNKPRSPVVVELSKVPLVQRGSANGL	689

65 Tables 9E-9L list the domain descriptions from DOMAIN analysis results against NOV9. This indicates that the NOV9 sequence has properties similar to those of other proteins known to contain this domain.

Table 9E. Domain Analysis of NOV9

gnl|Smart|smart00220, S TKc, Serine/Threonine protein kinases, catalytic domain; Phosphotransferases. Serine or threonine-specific kinase subfamily. (SEQ ID NO:98)
CD-Length = 256 residues, 100.0% aligned
Score = 237 bits (604), Expect = 2e-63

Query: 191 FSVHRIIGRGGFGEVYGCRAKDTGKMYAMKCLDKKRIKMKQGETLALNERIMLSLVSTGD 250
+ + ++|+| |+|| | |||+ |+| + |+++| |+| | | +| +|
5 Sbjct: 1 YELLEVLGKGAFGKVYLARDKKTGKLVAIKVIKKEKLKKKKRER-ILREIKILKKL---D 56

Query: 251 CPFIVCMSYAFHTPKLSFILDLMNGGDLHYHLSQHGVFSEADMRFYAAEIIILGLEHMHN 310
| || + | | | | +++ | || | + | | | + | | | +|+ | |++|+
10 Sbjct: 57 HPNIVKLYDVFEDDDKLYLVMEYCEGGDLFDLLKKRGRLEDEARFYARQILSALEYLHS 116

Query: 311 RFVYRDLKPANILLDEHGHVRISDLGLACDFSKKKPHAS--VGTHGYMAPEVLQKGVAY 368
+ +++| || | | | | | | | | | | | | | | + | | | | | | | | |
Sbjct: 117 QGIHRDLKPENILLDSGDHVKLADFLAKQLDSGGTLLTTFVGTPEYMAPEVL-LGKGY 175

Query: 369 DSSADWFSLGCMFLKLLRGHSPFRQHKTKDK-HEIDRMTLTMAVELPDSFSPELRSLLEG 427
+ | +| | | +|++| | | | | + | | | | | | | | | +|++
15 Sbjct: 176 GKAVDIWSLGVILYELLTGKPPFGDQLLALFKKIGKPPPPFPPPEWKISPEAKDLIK 235

Query: 428 LLQRDVNRRLGCLGRGAQEVKESPPF 453
| | +| +| | | | | | | | | | | | | | | | | | | | | | |
20 Sbjct: 236 LLVKDPEKRL-----TAEAELEHPFF 256

Table 9F. Domain Analysis of NOV9

gnl|Pfam|pfam00069, pkinase, Protein kinase domain. (SEQ ID NO:99)
CD-Length = 256 residues, 100.0% aligned
Score = 221 bits (562), Expect = 1e-58

Query: 191 FSVHRIIGRGGFGEVYGCRAKDTGKMYAMKCLDKKRIKMKQGETLALNERIMLSLVSTGD 250
+ + +| | | | | | + | | |++| +| | | + + | + | | | +| +|
25 Sbjct: 1 YELGEKLGSAFGKVYKGGHKDTGEIVAIKILKKRSLSEKKKRFL--REIQILRRLS--- 55

Query: 251 CPFIVCMSYAFHTPKLSFILDLMNGGDLHYHLSQHGVF-SEADMRFYAAEIIILGLEHMH 309
| || + | | | | +++ | || | | +| ++|+ | | + + | +|+ | |++|
30 Sbjct: 56 HPNIVRLLGVFEEDDHLYLVMEYMEGGDLFDYLRRNGLLSEKEAKKIALQILRGLEYLH 115

Query: 310 NRFVYRDLKPANILLDEHGHVRISDLGLACDF---SKKKPHASVGTHGYMAPEVLQKGV 366
+| +|+| | | | | | | | | +| +| | | | | | | | | | +|
35 Sbjct: 116 SRGIVHRDLKPENILLDENGTVKIADFLARKLESSSYEKLTTFVGTPEYMAPEVL-EGR 174

Query: 367 AYDSSADWFSLGCMFLKLLRGHSPFRQHKTKDKHEIDRMTLTMAVELPDSFSPELRSLLE 426
| | | +| | | +|++| | | | | ++ + + + | + | | | +|++
Sbjct: 175 GYSSKVDVWSLGVILYELLTGKLPFGIDPLEELFRIKERPRLRLPLPPNCSEELKDLIK 234

Query: 427 GLLQRDVNRRLGCLGRGAQEVKESPPF 453
| +| +| | | | | +| +| +|
40 Sbjct: 235 KCLNKDPEKRP-----TAKEILNHPWF 256

gnl|Smart|smart00233, PH, Pleckstrin homology domain.; Domain commonly found in eukaryotic signalling proteins. The domain family possesses multiple functions including the abilities to bind inositol phosphates, and various proteins. PH domains have been found to possess inserted domains (such as in PLC gamma, syntrophins) and to be inserted within other domains. Mutations in Brutons tyrosine kinase (Btk) within its PH domain cause X-linked agammaglobulinaemia (XLA) in patients. Point mutations cluster into the positively charged end of the molecule around the predicted binding site for phosphatidylinositol lipids. (SEQ ID NO:108)
CD-Length = 104 residues, 95.2% aligned
Score = 62.0 bits (149), Expect = 1e-10

15

```
Query: 539 IMHGYSKMGNPFLTQWQRRYFYFLFPNRLEW-----RGEGEAPQSLLTMEEIQ---SVEE 590
      |  |++ | + |++||| | | + + | + + + +
Sbjct: 2 IKEGWLLKKSSGGKKSWKRYFVLFNGVLLYYKSKKKSSSKPKGSIPLSGCTVREAPDS 61

Query: 591 TQIKERKCLLLKIRGGKQFILQCDSDPELVQWKKELRDA 629
      |++ | + | +|| +| + + || |
Sbjct: 62 DSDKKKNCFEIVTPDRKTLTLLQAESEERKEWVEALRKA 100
```

gnl|Pfam|pfam00169, PH, PH domain. PH stands for pleckstrin homology.
(SEQ ID NO:109)
CD-Length = 100 residues, 97.0% aligned
Score = 55.5 bits (132), Expect = 1e-08

25

```
Query: 539 IMHGYMSKMGNPFLLTQWQRRYFYLPNRLWE--RGEGEAPQSLLTMEEIQSVEETQIKE 595
      + |++ | +|++||+|| + | + + + | + + + + +
Sbjct: 2 VKEGWLLKKSTVKKKRWKRYFFLFNDVLIYYKDKKKSYPKGSIPLSGCSVEDVPDSEF 61

Query: 596 RKCLLLKIR--GGKQFILQCDSDPELVQWKELRDA 629
      ++ ++| | + ||| +|+ | | ++ |
Sbjct: 62 KRPNCFQLRSRDGKETFILQAESEEEERQDWIKAIQSA 98
```

gnl|Smart|smart00133, S_TK_X, Extension to Ser/Thr-type protein
kinases (SEQ ID NO:110)
CD-Length = 63 residues, 87.3% aligned
Score = 42.7 bits (99), Expect = 7e-05

Query: 454 RSLDWQMVFLQKYPPPLIPPRGEVNAADAFDIGSFDEEDTKGIKQEVAETVFDTINAETD 513
 | +|| + ++ || +| | +|| | | ++ | | +||
 Sbjct: 1 RGIDWDKLENKEIEPPFVPKVK-----SPTDTSNFDPEFT---EESPVLTVPDPPLSESD 52

5 Query: 514 RLE 516
 + |
 Sbjct: 53 QDE 55

10

Eukaryotic protein kinases are enzymes that belong to a very extensive family of proteins which share a conserved catalytic core common with both serine/threonine and tyrosine protein kinases. There are a number of conserved regions in the catalytic domain of protein kinases. In the N-terminal extremity of the catalytic domain there is a glycine-rich stretch of residues in the vicinity of a lysine residue, which has been shown to be involved in ATP binding. In the central part of the catalytic domain there is a conserved aspartic acid residue which is important for the catalytic activity of the enzyme.

The beta-adrenergic receptor kinase (beta ARK) catalyses the phosphorylation of the activated forms of the beta 2-adrenergic receptor (beta 2AR). The interaction between receptor and kinase is independent of second messengers and appears to involve a multipoint attachment of kinase and substrate with the specificity being restricted by both the primary amino acid sequence and conformation of the substrate. Kinetic, functional and sequence information reveals that rhodopsin kinase and beta ARK are closely related, suggesting they are members of a family of G-protein-coupled receptor kinases.

The beta-adrenergic signaling cascade is an important regulator of myocardial function. Significant alterations of this pathway are associated with several cardiovascular diseases, including congestive heart failure (CHF). CHF patients share several similar features, such as reduced cardiac contractility and neurohumoral activation to compensate the impaired cardiac function. In CHF patients, the cardiac renin-angiotensin (RA) system, receptors, GTP-binding proteins, and their effector molecules are inevitably exposed to chronically elevated neurohumoral stimulation. A widely recognized concept is that a chronic increase in such stimulation can desensitize target cell receptors and the post-receptor signal transducing pathway. Included in these alterations is increased activity and expression of G protein-coupled receptor kinases (GRKs), such as the beta-adrenergic receptor kinase (beta ARK1), which phosphorylate and desensitize beta-adrenergic receptors (beta ARs). A body of evidence is accumulating that suggests that GRKs, in particular beta ARK1, are critical determinants of cardiac function under normal conditions and in disease states. Transgenic mice with myocardial-targeted alterations of GRK activity have shown profound changes in the in vivo functional performance of the heart. Included in these studies is the compelling

finding that inhibition of beta ARK1 activity or expression significantly enhances cardiac function and potentiates beta AR signaling in failing cardiomyocytes. An uncoupling of beta2-adrenoceptors has been attributed to an increased activity and gene expression of beta-adrenergic receptor kinase in failing myocardium, leading to phosphorylation and uncoupling of receptors. The important physiological function of GRK2 as a modulator of the efficacy of GPCR signal transduction systems is exemplified by its relevance in cardiovascular physiopathology as well as by its emerging role in the regulation of chemokine receptors.

The disclosed NOV9 nucleic acid of the invention encoding a Beta-adrenergic receptor kinase-like protein includes the nucleic acid whose sequence is provided in Table 9A or a fragment thereof. The invention also includes a mutant or variant nucleic acid any of whose bases may be changed from the corresponding base shown in Table 9A while still encoding a protein that maintains its Beta-adrenergic receptor kinase-like activities and physiological functions, or a fragment of such a nucleic acid. The invention further includes nucleic acids whose sequences are complementary to those just described, including nucleic acid fragments that are complementary to any of the nucleic acids just described. The invention additionally includes nucleic acids or nucleic acid fragments, or complements thereto, whose structures include chemical modifications. Such modifications include, by way of nonlimiting example, modified bases, and nucleic acids whose sugar phosphate backbones are modified or derivatized. These modifications are carried out at least in part to enhance the chemical stability of the modified nucleic acid, such that they may be used, for example, as antisense binding nucleic acids in therapeutic applications in a subject. In the mutant or variant nucleic acids, and their complements, up to about 2 percent of the bases may be so changed.

The disclosed NOV9 protein of the invention includes the Beta-adrenergic receptor kinase-like protein whose sequence is provided in Table 9B. The invention also includes a mutant or variant protein any of whose residues may be changed from the corresponding residue shown in Table 9B while still encoding a protein that maintains its Beta-adrenergic receptor kinase-like activities and physiological functions, or a functional fragment thereof. In the mutant or variant protein, up to about 1 percent of the residues may be so changed.

The protein similarity information, expression pattern, and map location for the beta-adrenergic receptor kinase-like protein and the NOV9 proteins disclosed herein suggest that this beta-adrenergic receptor kinase may have important structural and/or physiological functions characteristic of the Ser/Thr protein kinases family. Therefore, the nucleic acids and proteins of the invention are useful in potential diagnostic and therapeutic applications and as a research tool. These include serving as a specific or selective nucleic acid or protein

diagnostic and/or prognostic marker, wherein the presence or amount of the nucleic acid or the protein are to be assessed, as well as potential therapeutic applications such as the following:

(i) a protein therapeutic, (ii) a small molecule drug target, (iii) an antibody target (therapeutic, diagnostic, drug targeting/cytotoxic antibody), (iv) a nucleic acid useful in gene therapy (gene delivery/gene ablation), and (v) a composition promoting tissue regeneration in vitro and in vivo (vi) biological defense weapon.

The NOV9 nucleic acids and proteins of the invention are useful in potential diagnostic and therapeutic applications implicated in various diseases and disorders described below and/or other pathologies. For example, the compositions of the present invention will have efficacy for treatment of patients suffering from heart failure, hypertension, secondary pathologies caused by heart failure and hypertension, and other diseases, disorders and conditions of the like. Additionally, the compositions of the present invention may have efficacy for treatment of patients suffering from conditions associated with the role of GRK2 in brain and in the regulation of chemokine receptors.. The NOV9 nucleic acid, or fragments thereof, may further be useful in diagnostic applications, wherein the presence or amount of the nucleic acid or the protein are to be assessed.

NOV9 nucleic acids and polypeptides are further useful in the generation of antibodies that bind immunospecifically to the novel substances of the invention for use in therapeutic or diagnostic methods. These antibodies may be generated according to methods known in the art, using prediction from hydrophobicity charts, as described in the "Anti-NOVX Antibodies" section below. For example the disclosed NOV9 protein have multiple hydrophilic regions, each of which can be used as an immunogen. In one embodiment, contemplated NOV9 epitope is from about amino acids 40 to 70. In another embodiment, the contemplated NOV9 epitope is from about amino acids 80 to 110. In further embodiments, the contemplated NOV9 epitope is from about amino acids 120 to 200, from about amino acids 220 to 245, from about amino acids 250 to 280, or from about amino acids 290 to 340. This novel protein also has value in development of powerful assay system for functional analysis of various human disorders, which will help in understanding of pathology of the disease and development of new drug targets for various disorders.

NOV10

A disclosed NOV10 nucleic acid of 3003 nucleotides (also referred to as AC058790_da25) encoding an alpha-mannosidase-like protein is shown in Table 10A. An open reading frame was identified beginning with an ATG initiation codon at nucleotides 57-

embodiments, NOV10 is also likely to be localized to the mitochondrial membrane space with a certainty of 0.4539, to the mitochondrial intermembrane space with a certainty of 0.4027, or to the lysosome (lumen) with a certainty of 0.2317.

Table 10B. Encoded NOV10 protein sequence (SEQ ID NO:26).

```
MAAAPFLKHWRRTTFERVEKFVSPYIYFTDCNLRGRLFGASCPVAVLSSFLTPERLPYQEAQVQDFRPAQVGDG
FGPTWWTQWFRVELTIPEAWVGQEVHLCWESDGEGLVWRDGEVQGLTKEGEKTSYVLTDRLGGERDPRSLTL
YVEVACNGLLGAGKGSMAAPDPEKMFQLSRAELAVFHRDVHMLLVLDLELLGIAKAQQLWVKSRYPGLYS
RIQEFACRGQFVPGGTWVEMDGNLPSGEAMVRQFLQGNFFLQEFQKMCSEFWLPDTFGYSAQLPQIMHGC
GIRRFLLTQKLSWNLVNSFPHTTFFWEGLDGSRVLVHFPPGDSYGMQGSVEEVLTQVANNRDKGRANHSALF
GFGDGGGPTQTMIDRLKRLSNTDGLPRVQLSSPRQLFSALESSEQLCTWVGELFLELHNGTYTTHAQIKK
GNRECEILHDEVELLSSALARSQAFLYPAAQLQHLWRLLLNQNPHDVTGSCIQMVAEEAMCHYEDIRSHG
NTLLSAAAAALCAGEPGPEGLLI VNTLPWKRIEVMALPKPGGAHSLALVTVP SMGYAPVPPPTSLQPLLPQQ
PVFVVQETDGSVTLDNIGIIRVKLDPTGRLTSLVLVSGREAI AEGAVGNQFVLFDDVPLYWDWDVMDYHLE
TRKPVLGQAGTLAVGTEGGLRGSWFLQISPNRSLSQEVVLDVGC PYVRFHTEVHWHEAHKFLKVEFFPARV
RSSQATYETIQFGLQRPHTYNTSWDWARFEVWAHRWMDLSEHGFLALLNDCKYGASVRGSILSLSLLRAPK
APDATADTGRHEFTYALMPHKGSFQDAGVIAAYSLNFP LLALPAPSPAPATSWSAFVSSPAVVLETVKQA
ESSPQRRSLVLRLYEAHGSHVDCWLHLSLPVQEA ILCDLLERPDPAGHLTSCQPPEAHLFSLPSAVPVARAS
ASATLSPWGWGFVCRRLWGLLISASPA
```

5 A search of sequence databases reveals that the NOV10 amino acid sequence has 764 of 771 amino acid residues (99%) identical to, and 767 of 771 amino acid residues (99%) similar to, the 1062 amino acid residue alpha-mannosidase protein from *Homo sapiens* (Q9UL64) (E = 0.0). Public amino acid databases include the GenBank databases, SwissProt, PDB and PIR.

10 NOV10 was derived from a pool of the following tissues: Adrenal gland, bone marrow, brain - amygdala, brain - cerebellum, brain - hippocampus, brain - substantia nigra, brain - thalamus, brain - whole, fetal brain, fetal kidney, fetal liver, fetal lung, heart, kidney, lymphoma - Raji, mammary gland, pancreas, pituitary gland, placenta, prostate, salivary gland, skeletal muscle, small intestine, spinal cord, spleen, stomach, testis, thyroid, trachea, uterus, Bone, Cervix, Chorionic Villus, Colon, Liver, Lung, Lymph node, Lymphoid tissue, 15 Ovary, Peripheral Blood, Skin, Stomach, Tonsils, Whole Organism. Thus, it is expressed in at least some of the above tissues. This information was derived by determining the tissue sources of the sequences that were included in the invention including but not limited to SeqCalling sources, Public EST sources, Genomic Clone sources, Literature sources, and/or 20 RACE sources.

The disclosed NOV10 polypeptide has homology to the amino acid sequences shown in the BLASTP data listed in Table 10C.

Table 10C. BLAST results for NOV10

Gene Index/ Identifier	Protein/ Organism	Length (aa)	Identity (%)	Positives (%)	Expect
ptnr:SPTREMBL-ACC:Q9UL64	ALPHA MANNOSIDASE 6A8B - Homo sapiens	1062	763/771 (99%)	767/771 (99%)	0.0
ptnr:SPTREMBL-ACC:Q9NTJ4	HYPOTHETICAL 115.8 KDA PROTEIN - Homo sapiens	1040	715/722 (99%)	718/722 (99%)	0.0
ptnr:TREMBLNEW-ACC:AAH16253	SIMILAR TO MANNOSIDASE, ALPHA, CLASS 2C, MEMBER 1	1039	635/730 (89%)	692/730 (94%)	0.0
ptnr:SWISSPROT-ACC:P21139	Alpha-mannosidase (EC 3.2.1.24)	1040	625/731 (85%)	661/731 (90%)	0.0
ptnr:SPTREMBL-ACC:Q13358	ALPHA-MANNOSIDASE - Homo sapiens	425	425/425 (100%)	425/425 (100%)	0.0

The homology between these and other sequences is shown graphically in the ClustalW analysis shown in Table 10D. In the ClustalW alignment of the NOV10 protein, as well as all other ClustalW analyses herein, the black outlined amino acid residues indicate regions of conserved sequence (*i.e.*, regions that may be required to preserve structural or functional properties), whereas non-highlighted amino acid residues are less conserved and can potentially be altered to a much broader extent without altering protein structure or function.

Table 10D. ClustalW Analysis of NOV10

1)	NOV10 (SEQ ID NO:26)
2)	ptnr: ALPHA MANNOSIDASE 6A8B - Homo sapiens (SEQ ID NO:73)
3)	ptnr: HYPOTHETICAL 115.8 KDA PROTEIN - Homo sapiens (SEQ ID NO:74)
4)	ptnr: SIMILAR TO MANNOSIDASE, ALPHA, CLASS 2C, MEMBER 1 (SEQ ID NO:75)
5)	ptnr: Alpha-mannosidase (EC 3.2.1.24) (SEQ ID NO:76)
NOV10	MAAAPFLKHW-RTTFERVEKF-VSPIYFTDCN-LRGRLEFGASCPVAVLSSFLTF-ERLPYQEAQVRC-----FRPAQVG 70
Q9UL64	MAAAPFLKHW-RTTFERVEKF-VSPIYFTDCN-LRGRLEFGASCPVAVLSSFLTF-ERLPYQEAQVRC-----FRPAQVG 70
Q9NTJ4	MAAAPFLKHW-RTTFERVEKF-VSPIYFTDCN-LRGRLEFGASCPVAVLSSFLTF-ERLPYQEAQVRC-----FRPAQVG 70
AAH16253	MAAAPFLKHW-RTTFERVEKF-VSPIYFTDCN-LRGRLEFGASCPVAVLSSFLTF-ERLPYQEAQVRC-----FRPAQVG 69
P21139	MAAAPFLKHW-RTTFERVEKF-VSPIYFTDCN-LRGRLEFGASCPVAVLSSFLTF-ERLPYQEAQVRC-----FRPAQVG 79
NOV10	C-SFGPTWWTWC-FRVELTIPEAVVQGEVHLCWE-SDGEGLVWRD-GEVQGLTK-----EGEKTSYVL-TDRLGERDPP 140
Q9UL64	C-SFGPTWWTWC-FRVELTIPEAVVQGEVHLCWE-SDGEGLVWRD-GEVQGLTK-----EGEKTSYVL-TDRLGERDPP 140
Q9NTJ4	C-SFGPTWWTWC-FRVELTIPEAVVQGEVHLCWE-SDGEGLVWRD-GEVQGLTK-----EGEKTSYVL-TDRLGERDPP 140
AAH16253	C-SFGPTWWTWC-FRVELTIPEAVVQGEVHLCWE-SDGEGLVWRD-GEVQGLTK-----EGEKTSYVL-TDRLGERDPP 139
P21139	C-SFGPTWWTWC-FRVELTIPEAVVQGEVHLCWE-SDGEGLVWRD-GEVQGLTK-----EGEKTSYVL-TDRLGERDPP 159
NOV10	S-LTLYVEVACNGLLGAGKGSMTAAPDPEKMF-QLSRAELAVF-----HRDVHMLLVD-LELLLGIAK 200
Q9UL64	S-LTLYVEVACNGLLGAGKGSMTAAPDPEKMF-QLSRAELAVF-----HRDVHMLLVD-LELLLGIAK 211
Q9NTJ4	S-LTLYVEVACNGLLGAGKGSMTAAPDPEKMF-QLSRAELAVF-----HRDVHMLLVD-LELLLGIAK 211
AAH16253	S-LTLYVEVACNGLLGAGKGSMTAAPDPEKMF-QLSRAELAVF-----HRDVHMLLVD-LELLLGIAK 210
P21139	S-LTLYVEVACNGLLGAGKGSMTAAPDPEKMF-QLSRAELAVF-----HRDVHMLLVD-LELLLGIAK 229
NOV10	ALYTANQMVNVCDAQPETFPVACALASRFFGQHGGSQHTIHATGHCHIDTAWLWPFKTVRKCARSWVTADQLMERNP 290
Q9UL64	ALYTANQMVNVCDAQPETFPVACALASRFFGQHGGSQHTIHATGHCHIDTAWLWPFKTVRKCARSWVTADQLMERNP 291
Q9NTJ4	ALYTANQMVNVCDAQPETFPVACALASRFFGQHGGSQHTIHATGHCHIDTAWLWPFKTVRKCARSWVTADQLMERNP 291
AAH16253	ALYTANQMVNVCDAQPETFPVACALASRFFGQHGGSQHTIHATGHCHIDTAWLWPFKTVRKCARSWVTADQLMERNP 290
P21139	ALYTANQMVNVCDAQPETFPVACALASRFFGQHGGSQHTIHATGHCHIDTAWLWPFKTVRKCARSWVTADQLMERNP 229
NOV10	-----AQOLEWVKSRYPGLYSRIQEFACRQGFVPVGGTGWVEMDGNLPSGEAMVROFLQGNFFLQEFQKMCSEFWLF 272
Q9UL64	-----AQOLEWVKSRYPGLYSRIQEFACRQGFVPVGGTGWVEMDGNLPSGEAMVROFLQGNFFLQEFQKMCSEFWLF 371

	Q9NTJ4	EF1FACSAQAQLEWVSRVPCLYSRIOEFACRCGFVPGVGTWVEMDQNLPSGSEAMVVRQFLOGQNFLLQEFQKMCSEFWLP	371
	AAH16253	EF1FACSAQAQLEWVSRVPCLYSRIOEFACRCGFVPGVGTWVEMDQNLPSGSEAMVVRQFLOGQNFLLQEFQKMCSEFWLP	370
	P21139	-----TLGDNQRNSFOAALY-----ANCMVNTCDP-AQPEPTAALHASFTAB-----PFCQRR-----	281
5	NOV10	DTFGYSAQLPQIMHGGCIRRFLLTKQLSNLNLVNSFPFHITTFWEGLDGSRLVLFHPPGDSYGMQGSVEEVLKTVANNRDKGF	352
	Q9UL64	DTFGYSAQLPQIMHGGCIRRFLLTKQLSNLNLVNSFPFHITTFWEGLDGSRLVLFHPPGDSYGMQGSVEEVLKTVANNRDKGF	451
	Q9NTJ4	DTFGYSAQLPQIMHGGCIRRFLLTKQLSNLNLVNSFPFHITTFWEGLDGSRLVLFHPPGDSYGMQGSVEEVLKTVANNRDKGF	451
	AAH16253	DTFGYSAQLPQIMHGGCIRRFLLTKQLSNLNLVNSFPFHITTFWEGLDGSRLVLFHPPGDSYGMQGSVEEVLKTVANNRDKGF	450
10	P21139	-----GSSQHTTITATGCHHIDTAWLN-----P-----FKETVRKCAF-----	314
	NOV10	ANHSFAFLFGFGDGGCGPTQTMLDRKLKRLSNTDGLPRVLQSSPROLPSALESDESQLCTWVGELFLELHNGTYTTHAQIKK	432
	Q9UL64	ANHSFAFLFGFGDGGCGPTQTMLDRKLKRLSNTDGLPRVLQSSPROLPSALESDESQLCTWVGELFLELHNGTYTTHAQIKK	531
	Q9NTJ4	ANHSFAFLFGFGDGGCGPTQTMLDRKLKRLSNTDGLPRVLQSSPROLPSALESDESQLCTWVGELFLELHNGTYTTHAQIKK	531
15	AAH16253	TNHSFLLFGFGDGGCGPTQTMLDRKLKRLSNTDGLPRVLQSSPROLPSALESDESQLCTWVGELFLELHNGTYTTHAQIKK	530
	P21139	-----SWS-----ITAVKLMK-----	325
	NOV10	GNRECEIRILHDVELLSSLALARSQFLYPAAQLQHLWRLLLIHOFHDVVGTSGCIQMVAAEAMCHYEDIRSHGNTLLSAAA	512
	Q9UL64	GNRECEIRILHDVELLSSLALARSQFLYPAAQLQHLWRLLLIHOFHDVVGTSGCIQMVAAEAMCHYEDIRSHGNTLLSAAA	611
20	Q9NTJ4	GNRECEIRILHDVELLSSLALARSQFLYPAAQLQHLWRLLLIHOFHDVVGTSGCIQMVAAEAMCHYEDIRSHGNTLLSAAA	611
	AAH16253	GNRECEIRILHDVELLSSLALARSQFLYPAAQLQHLWRLLLIHOFHDVVGTSGCIQMVAAEAMCHYEDIRSHGNTLLSAAA	610
	P21139	-----RN-----TFTFAACQATAB-----STOLEWVK-----NOY-----SS-----LYAQOLEFAN-----	365
	NOV10	AALCAGEPGPEGGLLIIVNTLPWKRIEVMALPKPGGAHSLALVTVPMSGYAPVPPTLSLOPLLPOOPVFVVOETDGSVTLDN	592
	Q9UL64	AALCAGEPGPEGGLLIIVNTLPWKRIEVMALPKPGGAHSLALVTVPMSGYAPVPPTLSLOPLLPOOPVFVVOETDGSVTLDN	691
	Q9NTJ4	AALCAGEPGPEGGLLIIVNTLPWKRIEVMALPKPGGAHSLALVTVPMSGYAPVPPTLSLOPLLPOOPVFVVOETDGSVTLDN	691
25	AAH16253	AALCAGEPGPEGGLLIIVNTLPWKRIEVMALPKPGGAHSLALVTVPMSGYAPVPPTLSLOPLLPOOPVFVVOETDGSVTLDN	690
	P21139	-----LRC-----Q-SVPGV-----	374
	NOV10	GIIRVKLDPTGRILTSVLVLVASGREIAIEGAVGNQFVLFFDDVPLYDAWDVMDYHLETRKPVLOAGTLAVGTGGGLRGSA	672
	Q9UL64	GIIRVKLDPTGRILTSVLVLVASGREIAIEGAVGNQFVLFFDDVPLYDAWDVMDYHLETRKPVLOAGTLAVGTGGGLRGSA	771
	Q9NTJ4	GIIRVKLDPTGRILTSVLVLVASGREIAIEGAVGNQFVLFFDDVPLYDAWDVMDYHLETRKPVLOAGTLAVGTGGGLRGSA	771
30	AAH16253	GIIRVKLDPTGRILTSVLVLVASGREIAIEGAVGNQFVLFFDDVPLYDAWDVMDYHLETRKPVLOAGTLAVGTGGGLRGSA	770
	P21139	-----GUTVMSGDN-----LPLSC-BAVVR-----QFTR-----QDGN-----	402
	NOV10	WFLLOISPNRSLSQEVVLDVGCPPYRFHTEVHWHEAHKFLKVEFPARVRSSQATYEIQFGHLQRPHTYNTSWDWARFEVK	752
	Q9UL64	WFLLOISPNRSLSQEVVLDVGCPPYRFHTEVHWHEAHKFLKVEFPARVRSSQATYEIQFGHLQRPHTYNTSWDWARFEVK	851
	Q9NTJ4	WFLLOISPNRSLSQEVVLDVGCPPYRFHTEVHWHEAHKFLKVEFPARVRSSQATYEIQFGHLQRPHTYNTSWDWARFEVK	851
35	AAH16253	WFLLOISPNRSLSQEVVLDVGCPPYRFHTEVHWHEAHKFLKVEFPARVRSSQATYEIQFGHLQRPHTYNTSWDWARFEVK	850
	P21139	-----FELQBF-----	408
40	NOV10	AHRWMDLSEHGFGALLNCKCYGASVRGSI LLSLLRAPKAPDADATDGRHEFTYALMPHKGSFQDAGVIOAAYSILNFP	832
	Q9UL64	AHRWMDLSEHGFGALLNCKCYGASVRGSI LLSLLRAPKAPDADATDGRHEFTYALMPHKGSFQDAGVIOAAYSILNFP	931
	Q9NTJ4	AHRWMDLSEHGFGALLNCKCYGASVRGSI LLSLLRAPKAPDADATDGRHEFTYALMPHKGSFQDAGVIOAAYSILNFP	931
45	AAH16253	AHRWMDLSEHGFGALLNCKCYGASVRGSI LLSLLRAPKAPDADATDGRHEFTYALMPHKGSFQDAGVIOAAYSILNFP	930
	P21139	-----	408
	NOV10	LALPAPSPAPATSWSAFVSVPVAVLETVKQAESSPORRSLVRLRYEAHGSVDCWHLSLPQOEAILCDLLERPDPAH	912
	Q9UL64	LALPAPSPAPATSWSAFVSVPVAVLETVKQAESSPORRSLVRLRYEAHGSVDCWHLSLPQOEAILCDLLERPDPAH	1011
50	Q9NTJ4	LALPAPSPAPATSWSAFVSVPVAVLETVKQAESSPORRSLVRLRYEAHGSVDCWHLSLPQOEAILCDLLERPDPAH	1011
	AAH16253	LALPAPSPAPATSWSAFVSVPVAVLETVKQAESSPORRSLVRLRYEAHGSVDCWHLSLPQOEAILCDLLERPDPAH	1010
	P21139	-----	408
	NOV10	LTSGQPPEAHLFSLPSAVPVARASASATLSFPGWGFVCRRLWGLLISASPA- 963	
	Q9UL64	LTSGQPPEAHLFSLPSAVPVARASASATLSFPGWGFVCRRLWGLLISASPA- 1062	
55	Q9NTJ4	LT-----IDRNRLKLTFSPE-----QVLS-----LLVYLQFPPH 1040	
	AAH16253	LT-----IDRNRLKLTFSPE-----QVRS-----LLVYLQFPPN 1039	
	P21139	-----	408

Table 10E lists the domain description from DOMAIN analysis results against NOV10. This indicates that the NOV10 sequence has properties similar to those of other proteins known to contain this domain.

Table 10E. Domain Analysis of NOV10					
Model	Description			Score	E-value
-----	-----			----	-----
Glyco_hydro_38 (InterPro)	Glycosyl hydrolases family 38			140.5	1e-39
(SEQ ID NO:111)					
Glyco_hydro_38: domain 1 of 2, from 230 to 332: score 89.2, E = 5.4e-25					
		*->vtGGWVMnDEAttHyedlldQlteGHqfLeenfGsdkvPkvgWsIDP			
		+ + + + +++ ++++ ++ + + ++ + + +++ +			
AC058790_d	230	VGGTIVVEMDGNLPSGEAMVRQFLQGQNFFLQEFG--KMCSEFWLPDT	274		
		FGHSatmPyLlraqaGfdgflIqRihYadKksfaetkgleFvWRqswslt			
		+ +++ ++ + + + + ++++++ + ++++ + + +			
AC058790_d	275	FGYSAQLPQIM-HGCGIRRFLLTQKLWNVLNVSFPPHHT---FFWE---GLD	317		

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                                gstdlfthmmpfysYd<-*
                                ||  +++| +| +||+
AC058790_d   318 GS-RVLVHFPPGDSYG           332
Glyco_hydro_38: domain 2 of 2, from 410 to 490: score 49.2, E = 1.7e-13
                   *->pYAdepdeGkPeYWTGYFTSRPalKrdRqlchlLrsaEilatqlsv
                   ++ +|++      | + |++|++++ | + +|++| |+++|+|++++ +
AC058790_d   410   TWVGELFL--ELHNGTYTTHAQIKKGNRECEILHDVELLSLALA 453
                   lagqskiegsyAikleklyeqleelRralaLfQHHDaiGTakqhVv<-*
                   ++++++      +      ||+ | +| | +|+| |++| |+++|+|+
AC058790_d   454 RS-AQFLYP-----A----QLQHLWRLLLLNQFHDVVTGSCIQMA 490

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Glycosyl hydrolases are key enzymes of carbohydrate metabolism. Lysosomal alpha-mannosidase is necessary for the catabolism of N-linked carbohydrates released during glycoprotein turnover. The enzyme catalyzes the hydrolysis of terminal, non-reducing alpha-D-mannose residues in alpha-D-mannosides, and can cleave all known types of alpha-mannosidic linkages. While alpha-mannosidases were classified as enzymes that process newly formed N-glycans or degrade mature glycoproteins, two endoplasmic reticulum (ER) alpha-mannosidases with previously assigned processing roles, have important catabolic activities. The ER/cytosolic mannosidase may be involved in the degradation of dolichol intermediates that are not needed for protein glycosylation, whereas the soluble form of Man9-mannosidase is responsible for the degradation of glycans on defective or malformed proteins that are specifically retained and broken down in the ER. The degradation of oligosaccharides derived from dolichol intermediates by ER/cytosolic mannosidase explains why cats and cattle with alpha-mannosidosis store and excrete some unexpected oligosaccharides containing only one GlcNAc residue. Similarly, the action of ER/cytosolic mannosidase, followed by the action of the recently described human lysosomal alpha(1 → 6)-mannosidase, together explain why alpha-mannosidosis patients store and excrete large amounts of oligosaccharides that resemble biosynthetic intermediates, rather than partially degraded glycans. The relative contributions of the lysosomal and extra-lysosomal catabolic pathways can be derived by comparing the ratio of trisaccharide Man beta (1 → 4)GlcNAc beta (1 → 4)GlcNAc to disaccharide Man beta (1 → 4)GlcNAc accumulated in tissues from goats with beta-mannosidosis. A similar determination in human beta-mannosidosis patients is not possible because the same intermediate, Man beta (1 → 4)-GlcNAc is a product of both pathways. Based on inhibitor studies with pyranose and furanose analogues, alpha-mannosidases may be divided into two groups. Those in Class 1 are (1 → 2)-specific enzymes like Golgi mannosidase I, whereas those in Class 2, like lysosomal alpha-mannosidase, can hydrolyse (1 → 2), (1 → 3) and (1 → 6) linkages. A similar classification has been derived from protein

sequence homologies. It is possible to speculate about their probable evolution from two primordial genes. The first would have been a Class 1 ER enzyme involved in the degradation of glycans on incompletely assembled or misfolded glycoproteins. The second would have been a Class 2 lysosomal enzyme responsible for turnover. Later, other alpha-mannosidases, with new processing or catabolic functions, would have developed from these, by loss or gain of critical insertion or retention sequences, to yield the full complement of alpha-mannosidases known today (Glycobiology 1994 Oct;4(5):551-66). Defects in the lysosomal alpha-mannosidase gene cause lysosomal alpha-mannosidosis (AM), a lysosomal storage disease characterized by the accumulation of unbranched oligo-saccharide chains. Depending on the clinical findings at the age of onset, a severe infantile (type I) and a mild juvenile (type II) form of alpha-mannosidosis are recognized. Furthermore, variability in clinical expression of the disease is seen within each type. Some of the disease features are: susceptibility to infection, vomiting, coarse features, macroglossia, flat nose, large clumsy ears, widely spaced teeth, large head, big hands and feet, tall stature, slight hepatosplenomegaly, muscular hypotonia, lumbar gibbus, radiographic skeletal abnormalities, dilated cerebral ventricles, lenticular opacities, hypogammaglobulinemia, 'storage cells' in the bone marrow, and vacuolated lymphocytes in the bone marrow and blood.

The disclosed NOV10 nucleic acid of the invention encoding a Alpha-mannosidase-like protein includes the nucleic acid whose sequence is provided in Table 10A or a fragment thereof. The invention also includes a mutant or variant nucleic acid any of whose bases may be changed from the corresponding base shown in Table 10A while still encoding a protein that maintains its Alpha-mannosidase-like activities and physiological functions, or a fragment of such a nucleic acid. The invention further includes nucleic acids whose sequences are complementary to those just described, including nucleic acid fragments that are complementary to any of the nucleic acids just described. The invention additionally includes nucleic acids or nucleic acid fragments, or complements thereto, whose structures include chemical modifications. Such modifications include, by way of nonlimiting example, modified bases, and nucleic acids whose sugar phosphate backbones are modified or derivatized. These modifications are carried out at least in part to enhance the chemical stability of the modified nucleic acid, such that they may be used, for example, as antisense binding nucleic acids in therapeutic applications in a subject. In the mutant or variant nucleic acids, and their complements, up to about 2 percent of the bases may be so changed.

The disclosed NOV10 protein of the invention includes the Alpha-mannosidase-like protein whose sequence is provided in Table 10B. The invention also includes a mutant or

variant protein any of whose residues may be changed from the corresponding residue shown in Table 10B while still encoding a protein that maintains its Alpha-mannosidase-like activities and physiological functions, or a functional fragment thereof. In the mutant or variant protein, up to about 1 percent of the residues may be so changed.

5 The protein similarity information, expression pattern, and map location for the alpha-mannosidase-like protein and the NOV10 protein disclosed herein suggest that this alpha-mannosidase-like protein may have important structural and/or physiological functions characteristic of the mannosidase protein family. Therefore, the nucleic acids and proteins of the invention are useful in potential diagnostic and therapeutic applications and as a research
10 tool. These applications include serving as a specific or selective nucleic acid or protein diagnostic and/or prognostic marker, wherein the presence or amount of the nucleic acid or the protein are to be assessed, as well as potential therapeutic applications such as the following: (i) a protein therapeutic, (ii) a small molecule drug target, (iii) an antibody target (therapeutic, diagnostic, drug targeting/cytotoxic antibody), (iv) a nucleic acid useful in gene therapy (gene
15 delivery/gene ablation), and (v) a composition promoting tissue regeneration in vitro and in vivo (vi) biological defense weapon.

 The NOV10 nucleic acids and proteins of the invention are useful in potential diagnostic and therapeutic applications implicated in various diseases and disorders described below and/or other pathologies. For example, the compositions of the present invention will
20 have efficacy for treatment of patients suffering from alpha-mannosidosis, beta-mannosidosis, other storage disorders, peroxisomal disorders such as zellweger syndrome, infantile refsum disease, rhizomelic chondrodysplasia (chondrodysplasia punctata, rhizomelic), and hyperpipecolic acidemia and other diseases, disorders and conditions of the like. Since mannosidoses are found not only in humans, but also in animals, the nucleic acids and proteins
25 of the this invention may be useful in treating animals with mannosidoses or other storage diseases, and other diseases, disorders and conditions of the like. Additionally, the compositions of the present invention may have efficacy for treatment of patients suffering from conditions associated with the role of GRK2 in brain and in the regulation of chemokine receptors.. The NOV10 nucleic acid, or fragments thereof, may further be useful in diagnostic
30 applications, wherein the presence or amount of the nucleic acid or the protein are to be assessed.

 NOV10 nucleic acids and polypeptides are further useful in the generation of antibodies that bind immunospecifically to the novel substances of the invention for use in therapeutic or diagnostic methods. These antibodies may be generated according to methods

known in the art, using prediction from hydrophobicity charts, as described in the “Anti-NOVX Antibodies” section below. For example the disclosed NOV10 protein have multiple hydrophilic regions, each of which can be used as an immunogen. In one embodiment, contemplated NOV10 epitope is from about amino acids 5 to 20. In another embodiment, the contemplated NOV10 epitope is from about amino acids 40 to 80. In further embodiments, the contemplated NOV10 epitope is from about amino acids 110 to 180, from about amino acids 200 to 230, from about amino acids 300 to 370, from about amino acids 375 to 450, from about amino acids 650 to 680, from about amino acids 690 to 770, from about amino acids 790 to 820, from about amino acids 850 to 880, or from about amino acids 900 to 920. This novel protein also has value in development of powerful assay system for functional analysis of various human disorders, which will help in understanding of pathology of the disease and development of new drug targets for various disorders.

NOV11

NOV11 includes three novel C1q-related factor-like proteins disclosed below. The
15 disclosed sequences have been named NOV11a, NOV11b, and NOV11c. Single nucleotide
polymorphism data is discussed below in Example 4.

NOV11a

A disclosed NOV11a nucleic acid of 805 nucleotides (also referred to as
20 GM57107065_da1) encoding an C1q-related factor-like protein is shown in Table 11A. An
open reading frame was identified beginning with an ATG initiation codon at nucleotides 83-
85 and ending with a TGA codon at nucleotides 797-799. Putative untranslated regions are
upstream from the initiation codon and downstream from the termination codon.

Table 11A. NOV11a nucleotide sequence (SEQ ID NO:27).

GAGTGAGGAAGATTGCTGGCCCTGGCAGCGTCGCGGCTGAGCCGCCGCAAGAGGGTGCGGGCGCGGCCGCTCGGAGTG
CCATGGTGCTGCTGCTGCTGGTGGCCATCCCGCTGCTGGTGACAGCTCCCGCGGGCCAGCGCACTACGAGATCTGTGGGT
CGCTCGCGCATGGTGTGCGACCCGCTATGGCCCTGGTCCGAGCGGCGCGCTGCTTCGTGACCCCCCTTCC
GCCAGGCGCAAGGGAGAGTGGGCGGTGCGGAAAGCAGGCTTGAGGGGGCCCCCGTGAACACAGTGTCAAAGAGGG
CCCCAGGAGAACCCGGCAGGCCAGGCCCCCCCGGGCCCTCCGGTTCAGAGTCCGGCGGGGTGGCGCCCCGCTGCCGGCTAC
GTGCTCTGCATGCTTTCTACGCGGGCCTGCGCGGCCCCACGAGGGTTACGAGGTCTGCGCTCTCAGCAGCTGGTGAC
CAACGTGGGCAACGCTTACGAGGCACGCGCGCAAGTTTACTTGCCCAATGCCAGGCGTCTACTTCTTCGTTACCACG
TGCTCATGCGCGGCGGCGACGGCACCAGCATGTGGGCCGACCTCATGAAGAACGGACAGGTCCGGGCCAGCGCCATTGCT
CAGGACGCGGACAGAACTACGACTACGCCAGCAACAGCGTCATTCTGCACCTGGACGTGGGCGACAGGTCTTCATCAA
GCTGGACGCGGGAAAGTGACCGGCGGCAACCAACAAGTACAGCACCTTCTCCGGCTTCATCATCTACCCCGACTGAG
CCGGC

In a search of public sequence databases, the NOV11a nucleic acid, located on chromosome 12, has 565 of 787 bases (71%) identical to a C1q- related factor mRNA from

Homo sapiens, (GENBANK-ID: AF095154) ($E = 9.9e^{-68}$). Public nucleotide databases include all GenBank databases and the GeneSeq patent database.

Table 11C. NOV11b nucleotide sequence (SEQ ID NO:29).

GAGTGAGGAAGATTGCTGGCCCTGGCAGCGTCGCGGCTGAGCCGCGCAAGAGGGTGGCGGGCGCGGCCGTCGGAGTGG
 CCATGGTGCTGCTGCTGCTGGTGGCCATCCCCTGCTGGTGACAGCTCCCGCGGGCCAGCGCACTACGAGATGCTGGGT
 CGTGCCCGCATGGTGTGCGACCCCGCATGGGCCCCGTGGCCCTGGTCCGGACGGCGCGCTGCTTCCGTGCCCCCTTCCC
 GCCAGGCGCAAGGAGAGGTGGGCGGGCGGGAAAGCAGGCCTGCGGGGCCCCCTGGACCACCAGGTCCAAGAGGGC
 CCCCAGGAGAACCCGGCAGGCCAGGCCCCCCGGGCCCTCCCGGTCCAGGTCCGGGCGGGGTGGCGCCCGCTGCCGGCTAC
 GTGCTCGCATTGCTTTCTACGCGGGCTGCGGCGGCCCCACGAGGGTTACGAGGTGCTGCGCTTCGACGACGTGGTGAC
 CAACGTGGGCAACGCTACGAGGCAGCCAGCGCAAGTTTACTTGCCCCATGCCAGGCGTCTACTTCTTCGCTTACCACG
 TGCTCATGCGCGGCGGCGACGGCACCAGCATGTGGGCCGACCTCATGAAGAACGGACAGGTCCGGGCCAGCGCCATTGCT
 CAGGACGCGGACCAGAACTACGACTACGCCAGCAACAGCGTCATTCTGCACCTGGACGTGGGCGACGAGGTCTTCATCAA
 GCTGGACGGCGGAAAGTGACGGCGGCAACACCAACAAGTACAGCACCTTCTCCGGCTTCATCATCTACCCCGACTGAG
 CCGGC

In a search of public sequence databases, the NOV11a nucleic acid, located on
 chromosome 17q21, has 565 of 787 bases (71%) identical to a C1q- related factor mRNA from
 5 *Homo sapiens*, (GENBANK-ID: AF095154) ($E = 1.9e^{-68}$). Public nucleotide databases include
 all GenBank databases and the GeneSeq patent database.

The disclosed NOV11b polypeptide (SEQ ID NO:30) encoded by SEQ ID NO:29 has
 238 amino acid residues and is presented in Table 11D using the one-letter amino acid code.
 The SignalP, Psort and/or Hydropathy profile for NOV11b predict that this sequence has a
 10 signal peptide and is likely to be localized extracellularly with a certainty of 0.5374, as
 expected by a protein similar to the C1q complement component. In other embodiments,
 NOV11b is also likely to be localized to the microbody (peroxisome) with a certainty of
 0.1199, to the endoplasmic reticulum (membrane) with a certainty of 0.1000, and to the
 endoplasmic reticulum (lumen) with a certainty of 0.1000. The most likely cleavage site for
 15 NOV11b is between positions 15 and 16: VHS-SR.

Table 11D. Encoded NOV11b protein sequence (SEQ ID NO:30).

MVLLLLVAIPLLHSSRGPAHYEMLGRCRMVCDPHGPRGPGPDGAPASVPPFPAGKGEVGRRKAGLRGPP
 GPPGPRGPPGPRGPPGPPGPGGVAAGYVPRIAFYAGLRRPHEGYEVLRFDDVVTVNGNAYEAASG
 KFTCPMPGVYFFAYHVLMRGGDGTSMWADLMKNGQVRASAIQDADQNYDYASNSVILHLDVGDEVFIKLDG
 GKVHGGNTNKYSTFSGFI IYPD

A search of sequence databases reveals that the NOV11b amino acid sequence has 184
 of 258 amino acid residues (71%) identical to, and 198 of 258 amino acid residues (76%)
 20 similar to, the 258 amino acid residue C1q-related factor precursor protein from *Homo sapiens*
 (075973) ($E = 7.1 e^{-91}$). Public amino acid databases include the GenBank databases,
 SwissProt, PDB and PIR.

NOV11b is expressed in at least some of the following tissues: adrenal gland, bone
 marrow, brain - amygdala, brain - cerebellum, brain - hippocampus, brain - substantia nigra,

brain - thalamus, brain -whole, fetal brain, fetal kidney, fetal liver, fetal lung, heart, kidney, lymphoma - Raji, mammary gland, pancreas, pituitary gland, placenta, prostate, salivary gland, skeletal muscle, small intestine, spinal cord, spleen, stomach, testis, thyroid, trachea, uterus, right cerebellum. This information was derived by determining the tissue sources of the sequences that were included in the invention including but not limited to SeqCalling sources, Public EST sources, Literature sources, and/or RACE sources.

NOV11c

A disclosed NOV11c nucleic acid of 887 nucleotides (also referred to as CG54503-03) encoding a novel C1q-related factor-like protein is shown in Table 11E. An open reading frame was identified beginning with an ATG initiation codon at nucleotides 19-21 and ending with a TAG codon at nucleotides 880-882. Putative untranslated regions are underlined and are found upstream from the initiation codon and downstream from the termination codon.

Table 11E. NOV11c nucleotide sequence (SEQ ID NO:217).

GTCCGGCTACTCTTGGCCATGGCGCTCGGGCTGCTCATCGCCGTGCCGCTGCTGCTGCAGGCGGCGCCCCGAGGCGCCGC
GCACTATGAGATGATGGGCACCTGCCGCATGATCTGCGACCCCTTACACTGCCGCGCCCGGCGGGGAGCCCCGGGTGCAA
AGGCGCAGCCACCCGACCCAGCACCGCCGCCCTGGAAGTCATGCAGGACCTCAGCGCCAACCTCCTCCTCCTTTCATC
CAGGGACCCAAGGGCGACCCGGGGCGACCGGGCAAGCCAGGGCCGCGGGGGCCCCCTGGAGAGCCGGGCCCGCTGGACC
CAGGGGCCCTCCGGGAGAGAAGGGCGACTCGGGGAGGCCGGGGTCCAGGGCTGCAACTGACGGCGGGCAGGCCAGCG
GCGTCGGGGTGGTGGGCGGCGGGGGCGGGGTAGGTGGCGATTCCGAGGGTGAAGTGACCAAGTGCCTGAGCGCCACCTTC
AGCGGCCCAAGATCGCCTTCTATGTGGGTCTCAAGAGCCCCCAGGAAGGCTATGAGGTGCTGAAGTTCGATGACGTGGT
CACCAACCTCGGCAATCACTATGACCCACCAAGGGCAAGTTCAGCTGCCAGGTACGCGGCATCTACTTCTTCACTACC
ACATCCTCATGCGCGGCGGCGACGGCACCAGCATGTGGGCGGACCTCTGCAAGAACGGGCAGGTCCGGGCGAGCGCCATT
GCACAGGACGCGGACCAAGTACGACTACGCCAGTAACAGCGTGGTGTGCACTTGGATTACGGGGACGAAGTGTATGT
GAAGCTGGATGGCGGGAAGGCTACGGAGGCAATAATAACAAGTACAGCACGTTCTCGGGCTTCTTCTGTACCCGATT
AGGGGCG

In a search of public sequence databases, the NOV11c nucleic acid has 538 of 777 bases (69%) identical to a gb:GENBANK-ID:AF095154|acc:AF095154.1 mRNA from *Homo sapiens* (*Homo sapiens* C1q-related factor mRNA, complete cds) ($E = 8.0e^{-58}$). Public nucleotide databases include all GenBank databases and the GeneSeq patent database.

The disclosed NOV11c polypeptide (SEQ ID NO:218) encoded by SEQ ID NO:217 has 287 amino acid residues and is presented in Table 11D using the one-letter amino acid code. The SignalP, Psort and/or Hydropathy profile for NOV11c predict that this sequence has a signal peptide and is likely to be localized extracellularly with a certainty of 0.3798, as expected by a protein similar to the C1q complement component. In other embodiments, NOV11c is also likely to be localized to the endoplasmic reticulum (membrane) with a certainty of 0.1000, to the endoplasmic reticulum (lumen) with a certainty of 0.1000, and to

the lysosome (lumen) with a certainty of 0.1000. The most likely cleavage site for NOV11c is between positions 21 and 22: GAA-HY.

Table 11D. Encoded NOV11c protein sequence (SEQ ID NO:218).

MALGLLIAVPLLLQAAPRGAAHYEMMGTCRMI CDPYTAAPGGEPGAKAQPPGPSTAALVMDLSANPPPP
FIQGPKGDPGRPGKPGPRGPPGEPGPPGPRGPPGEGKDSGRPGLPGLQLTAGTASGVGVGGAGVGGDSEG
EVTALSATFSGPKIAFYVGLKSPHEGYEVLKFDDVVTNLGNHYDPTTGKFSCQVRGIYFFTYHILMRGGDG
TSMWADLCKNGQVRASAI AQDADQNYDYASNSVVLHLD SGDEVYVKLDGGKAHGNNNKYSTFSGFLLYPD

5 A search of sequence databases reveals that the NOV11c amino acid sequence has 161 of 217 amino acid residues (74%) identical to, and 177 of 217 amino acid residues (81%) similar to, the 255 amino acid residue ptnr:TREMBLNEW-ACC:BAB15806 protein from *Mus musculus* (Mouse) (Gliacolin) ($E = 1.9 \times 10^{-85}$). Public amino acid databases include the GenBank databases, SwissProt, PDB and PIR.

10 NOV11c is expressed in at least brain. Expression information was derived from the tissue sources of the sequences that were included in the derivation of the sequence of CuraGen Acc. No. CG54503-03.

The disclosed NOV11a polypeptide has homology to the amino acid sequences shown in the BLASTP data listed in Table 11E.

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Table. 11E. BLAST results for NOV11a

Gene Index/ Identifier	Protein/ Organism	Length (aa)	Identity (%)	Positives (%)	Expect
Ptnr: SWISSPROT-ACC: 075973	C1q-related factor precursor - Homo sapiens	258	184/258 (71%)	198/258 (76%)	9.1e-91
ptnr:SWISSPROT- ACC:088992	C1q-related factor precursor - Mus musculus	258	156/216 (72%)	166/216 (76%)	1.8e-78
ptnr:SWISSPROT- ACC:Q9ESN4	Gliacolin precursor - Mus musculus	155	153/209 (73%)	165/209 (78%)	1.3e-77
ptnr:SWISSPROT- ACC:P02746	Complement C1q subcomponent	251	90/239 (37%)	124/239 (51%)	1.3e-29
ptnr:TREMBLNEW- ACC:AAH08983	COMPLEMENT COMPONENT 1	253	90/239 (37%)	124/239 (51%)	1.3e-29

The homology between these and other sequences is shown graphically in the ClustalW analysis shown in Table 11F. In the ClustalW alignment of the NOV11 protein, as well as all other ClustalW analyses herein, the black outlined amino acid residues indicate regions of conserved sequence (*i.e.*, regions that may be required to preserve structural or

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functional properties), whereas non-highlighted amino acid residues are less conserved and can potentially be altered to a much broader extent without altering protein structure or function.

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Table 11F. ClustalW Analysis of NOV11

1) NOV11a (SEQ ID NO:28)
2) NOV11b (SEQ ID NO:30)
3) NOV11c (SEQ ID NO:218)
4) ptnr: C1q-related factor precursor - Homo sapiens (SEQ ID NO:77)
5) ptnr: C1q-related factor precursor - Mus musculus (SEQ ID NO:78)
6) ptnr: Gliacolin precursor - Mus musculus (SEQ ID NO:79)
7) ptnr: Complement C1q subcomponent (SEQ ID NO:80)

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10 20 30 40 50 60
NOV11a
NOV11b
NOV11c
O75973
O88992
Q9ESN4
P02746
AAH08983
70 80 90 100 110 120
NOV11a
NOV11b
NOV11c
O75973
O88992
Q9ESN4
P02746
AAH08983
130 140 150 160 170 180
NOV11a
NOV11b
NOV11c
O75973
O88992
Q9ESN4
P02746
AAH08983
190 200 210 220 230 240
NOV11a
NOV11b
NOV11c
O75973
O88992
Q9ESN4
P02746
AAH08983
250 260 270 280 290
NOV11a
NOV11b
NOV11c
O75973
O88992

Q9ESN4 AIAQDADQNYDYASNSVILHLDAGDEVFIKLDGGKAHGCNSNKYSTFSGFIIYSD--- 258
P02746 TFCDYAYNTFQVTITGGMVLKLEQGENVFLQATDKNSLLCMEGANSIFSGFLLFPDMEA 251
AAH08983 TFCDYAYNTFQVTITGGMVLKLEQGENVFLQATDKNSLLCMEGANSIFSGFLLFPDMEA 253

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Tables 11E-11F list the domain descriptions from DOMAIN analysis results against NOV11. This indicates that the NOV11 sequence has properties similar to those of other proteins known to contain this domain.

Table 11E. Domain Analysis of NOV11

gnl|Smart|smart00110, C1q, Complement component C1q domain.; Globular domain found in many collagens and eponymously in complement C1q. When part of full length proteins these domains form a 'bouquet' due to the multimerization of heterotrimers. The C1q fold is similar to that of tumour necrosis factor. (SEQ ID NO:104)
CD-Length = 132 residues, 99.2% aligned
Score = 113 bits (283), Expect = 1e-26

Query: 108 PRIAFYAGL--RRPHEGYEVLRFDDVVTNVGNAYEAASGKFTCPMPGVYFFAYHVLMRGG 165
|| || || + + || | + | | + + || || | + || | + || +
Sbjct: 2 PRSAFSVIRSTNRPPPPGQPVRFDKVLYNQGHYDPSTGKFTCPVPGVYFYSYHIESK-- 59
Query: 166 DGTSMWADLMKNGQVRASAI AQDADQNYDYASNSVILHLDVGDEVFIKLDGGKVHG--GNT 224
| ++ || || | + | || + | || | || + || + || |
Sbjct: 60 -GRNVKVSMLMNGIQVMRECEYQKGLYQVASGGALLQLRQGDQVWLELDDKKNGLYAGE 118
Query: 225 NKYSTFSGFIIYPD 238
|| || || || ++ ||
Sbjct: 119 EVDSTFSGFLLFPD 132

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Table 11F. Domain Analysis of NOV11

gnl|Pfam|pfam00386, C1q, C1q domain. C1q is a subunit of the C1 enzyme complex that activates the serum complement system. (SEQ ID NO:112)
CD-Length = 125 residues, 100.0% aligned
Score = 102 bits (253), Expect = 3e-23

Query: 111 AFYAGLR-RPHEGYEVLRFDDVVTNVGNAYEAASGKFTCPMPGVYFFAYHVLMRGGDGTS 169
|| | || + + || + | | + | + || || | + || + | + | + || +
Sbjct: 1 AFTAIRSTRPPAPGQPVIFDEVLYNQGHYDPATGKFTCPVPGLYYFNHVSSEK--GTN 57
Query: 170 MWADLMKNGQVRASAI AQDADQNYDYASNSVILHLDVGDEVFIKLDGGKVHG--GNTNKY 227
+ || + || | + | || + | || | || + || + || + || + || +
Sbjct: 58 VCVSLMRNGVPVMSFCDEYAKGTQVASGGAVLQLRQGDRVWLELDDKQTNGLLGEGGVH 117
Query: 228 STFSGFII 235
| || || ++
Sbjct: 118 SVFSGFLL 125

The first component of complement system is a calcium-dependent complex of the 3 subcomponents C1q, C1r, and C1s. Subcomponent C1q binds to immunoglobulin complexes

with resulting serial activation of C1r (enzyme), C1s (proenzyme) and the other 8 components of complement. It contains collagen like domains. It has been shown that fibronectin binds to C1q in the same manner that it binds collagen. A major function of the fibronectins is in the adhesion of cells to extracellular materials such as solid substrata and matrices. Because
5 fibronectin stimulates endocytosis and promotes the clearance of particulate material from the circulation, the results suggest that fibronectin functions in the clearance of C1q-coated material such as immune complexes or cellular debris. Many examples of deficiencies of C1q have been reported, most of them associated with systemic lupus erythematosus or glomerulonephritis.

10 The complement system plays a paradoxical role in the development and expression of autoimmunity in humans. The activation of complement in SLE contributes to tissue injury. In contrast, inherited deficiency of classic pathway components, particularly C1q, is probably associated with the development of SLE. This leads to the hypothesis that a physiologic action of the early part of the classic pathway protects against the development of SLE and implies
15 that C1q may play a key role in this respect. C1q-deficient (C1qa^{-/-}) mice have been shown to have increased mortality and higher titers of autoantibodies, compared with strain-matched controls. Of the C1qa^{-/-} mice, 25% have been shown to have glomerulonephritis with immune deposits and multiple apoptotic cell bodies. Among mice without glomerulonephritis, there were significantly greater numbers of glomerular apoptotic bodies in C1q-deficient mice
20 compared with controls. The phenotype associated with C1q deficiency was modified by background genes. These findings are compatible with the hypothesis that C1q deficiency causes autoimmunity by impairment of the clearance of apoptotic cells.

The C1q-related factor is a recently discovered protein which has homology to C1q. Since this is a relatively new discovery, very little is known about its function. But conclusions
25 could clearly be derived from its expression pattern and its homology to C1q. Based on its expression pattern it has been suggested that this protein may be involved in motor function. The functions of C1q have been described above and include role in binding to immunoglobulin complexes, cell adhesion, autoimmunity and apoptosis, among others.

The disclosed NOV11 nucleic acid of the invention encoding a C1q-related factor-like
30 protein includes the nucleic acid whose sequence is provided in Table 11A, 11C, or a fragment thereof. The invention also includes a mutant or variant nucleic acid any of whose bases may be changed from the corresponding base shown in Table 11A or 11C while still encoding a protein that maintains its C1q-related factor-like activities and physiological functions, or a fragment of such a nucleic acid. The invention further includes nucleic acids whose sequences

are complementary to those just described, including nucleic acid fragments that are complementary to any of the nucleic acids just described. The invention additionally includes nucleic acids or nucleic acid fragments, or complements thereto, whose structures include chemical modifications. Such modifications include, by way of nonlimiting example, modified bases, and nucleic acids whose sugar phosphate backbones are modified or derivatized. These modifications are carried out at least in part to enhance the chemical stability of the modified nucleic acid, such that they may be used, for example, as antisense binding nucleic acids in therapeutic applications in a subject. In the mutant or variant nucleic acids, and their complements, up to about 29 percent of the bases may be so changed.

The disclosed NOV11 protein of the invention includes the C1q-related factor-like protein whose sequence is provided in Table 11B or 11D. The invention also includes a mutant or variant protein any of whose residues may be changed from the corresponding residue shown in Table 11B or 11D while still encoding a protein that maintains its C1q-related factor-like activities and physiological functions, or a functional fragment thereof. In the mutant or variant protein, up to about 29 percent of the residues may be so changed.

The protein similarity information, expression pattern, and map location for the C1q-related factor-like protein and nucleic acid disclosed herein suggest that this C1q-related factor may have important structural and/or physiological functions characteristic of the C1q family. Therefore, the nucleic acids and proteins of the invention are useful in potential diagnostic and therapeutic applications and as a research tool. These include serving as a specific or selective nucleic acid or protein diagnostic and/or prognostic marker, wherein the presence or amount of the nucleic acid or the protein are to be assessed, as well as potential therapeutic applications such as the following: (i) a protein therapeutic, (ii) a small molecule drug target, (iii) an antibody target (therapeutic, diagnostic, drug targeting/cytotoxic antibody), (iv) a nucleic acid useful in gene therapy (gene delivery/gene ablation), and (v) a composition promoting tissue regeneration in vitro and in vivo (vi) biological defense weapon.

The nucleic acids and proteins of the invention are useful in potential diagnostic and therapeutic applications implicated in various diseases and disorders described below and/or other pathologies. Based on the TaqMan data, the compositions of the present invention, will have efficacy for treatment of patients suffering from: cancer of the colon, kidney, ovary, skin and brain. Since it is over expressed in cell lines derived from these tissues it can also be used as a diagnostic marker for cancer in these tissues. The expression of the novel gene of this invention upon activation of HUVEC and the homology of the novel protein of this invention to C1q may indicate that it is secreted by endothelial cells in areas of inflammation where Th1

cells are infiltrating the inflammation site such as Rheumatoid Arthritis and Inflammatory Bowel Disease. Based on its homology to C1q, the novel protein could be either pro-inflammatory activating the complement cascade and be a useful target for a monoclonal antibody to block this effect. Alternatively, this protein may act as a competitor of C1q and so act to down regulate complement mediated damage of endothelial cells. In this case it could be used as a protein therapeutic. IFN gamma also induces production of this protein by airway epithelial cell lines NCI-H292 and dermal fibroblasts indicating again that it may play a role in Th1 inflammatory diseases such as rheumatoid arthritis, multiple sclerosis, inflammatory bowel diseases and psoriasis and other diseases, disorders and conditions of the like. Because of its high homology to C1q-related factor, this novel protein may also play a role in disorders of the nervous system involved in motor function.

Based on its homology to C1q, the novel protein of invention may also play a role in the pathogenesis of systemic lupus erythematosus and glomerulonephritis and therefore could be used for detection and treatment of these diseases. Thus this protein may be involved in autoimmunity. Since the novel protein of invention has a Collagen triple helix repeat domain, it is likely that this protein may be involved in collagen related disorders and processes such as but not limited to osteogenesis, rheumatoid arthritis and osteoarthritis.

Finally, presence of somatotropin-like domain in the novel protein of invention suggests that it may have somatotropin (growth hormone) like function and behave as a growth hormone and be useful in control of growth and development/differentiation related functions such as but not limited maturation, lactation and puberty. Because of the involvement of growth hormone in many different physiologic functions, the novel protein may be involved in causing osteoporosis, obesity, aging and reproductive malfunction and hence could be used in treatment and/or diagnosis of these disorders.

The NOV11 nucleic acid, or fragments thereof, may further be useful in diagnostic applications, wherein the presence or amount of the nucleic acid or the protein are to be assessed.

NOV11 nucleic acids and polypeptides are further useful in the generation of antibodies that bind immunospecifically to the novel substances of the invention for use in therapeutic or diagnostic methods. These antibodies may be generated according to methods known in the art, using prediction from hydrophobicity charts, as described in the "Anti-NOVX Antibodies" section below. For example the disclosed NOV11 protein have multiple hydrophilic regions, each of which can be used as an immunogen. In one embodiment, contemplated NOV11 epitope is from about amino acids 20 to 120. In another embodiment,

the contemplated NOV11 epitope is from about amino acids 130 to 150. In further embodiments, the contemplated NOV11 epitope is from about amino acids 170 to 210, or from about amino acids 220 to 240. This novel protein also has value in development of powerful assay system for functional analysis of various human disorders, which will help in understanding of pathology of the disease and development of new drug targets for various disorders.

NOV12

A disclosed NOV12 nucleic acid of 5895 nucleotides (also referred to as SC132340676_A) encoding an plexin-1-like protein is shown in Table 12A. An open reading frame was identified beginning with an ATG initiation codon at nucleotides 77-79 and ending with a TGA codon at nucleotides 5798-5800. The putative untranslated regions are underlined and are upstream from the initiation codon and downstream from the termination codon in Table 12A. The start and stop codons are in bold letters.

Table 12A. NOV12 nucleotide sequence (SEQ ID NO:31).

CAGGGCTGAAGCTCCTGGCACCATGATGCTCACCCAGCAGGACCAGAGCACCGAGGCCCAAGGCCCCAGCCTGCCATGCGCTGCCACCGCGGAGCCTGCAGGTGCTCCTGCTGCTGCTGCTGTTGCTGCTGCTGCTGCCGGGCATGTGGGCTGAGGCA
GGCTTGCCACAGGCGAGGCGGGGTTACAGCCCCCTTCCGCACTTCTCGGCCAGCGACTGGGGCCTCACCCACCTAGT
GGTGCAAGCAGACAGGCGAGGTGATGTGGGCGCAGTGAACCGCATCTATAAGCTGTGCGGGAACTGACACTGCTGC
GGGCCCCAGTCACGGGCCCTGTGGAGGACAACGAGAAGTGCTACCCGCGGCCAGCGTGCACTCTGCCCCACGGCCTG
GGCAGTACTGACAACGTCACAAGCTGCTGCTGCTGGAATATGCCGCTAACCGCCTGCTGGCCTGTGGCAGCGCCTCCCA
GGGCATCTGCCAGTTCCTGCGCTGAGACGATCTCTTCAAACCTGGGTGAGCCACACCACCGTAAGGAGCACTACCTGTCCA
GCGTGAGGAGGAGGAGCAGCATGGCGGGCGTGCTCATTTGCCGGGCCACCGGGCCAGGGCCAGGCCAAGCTCTTCGTGGGC
ACACCCATCGATGGCAAGTCCGAGTACTTCCCCACACTGTCCAGCCGTCGGCTCATGGCCAAACGAGGAGGATGCCGACAT
GTTCCGCTTCGTGTACAGGATGAGTTTGTGTCTACAGCTCAAGATCCCTTCGGACACGCTGTCCAAGTTCCTGGCCT
TTGACATCTACTATGTGTACAGCTTCCGCGAGCAGAGTTTGTCTACTACCTACGCTGACGCTAGACACACAGCTGACC
TCGCCATGATGCCGCGCGGAGCACTTCTTACGTCGAAGATCGTGCGGCTCTGTGTGGACACCCAAATTTACTCTGTA
CGTTGAGTTCCCCATTGGCTGCGAGCAGGCGGGTGTGGAGTACCGCCTGGTGCAGGATGCCCTACCTGAGCCGGCCCGGCC
GTGCCCTGGCCCAACAGCTGGGCTGGCTGAGGACGAGGACGTGCTGTCACTGTGTTCCGCCAGGGCCAGAAGAACCGC
GTGAAGCCACCAAGGAGTCAGCACTGTGCCTGTTACGCTCAGGGCCATCAAGGAGAAGATTAAGGAGCGCATCCAGTCT
CTGTACCGTGTGAGGCAAGCTCTCCCTGCCGTGGCTGCTCAACAAGGAGCTGGGCTGCATCAACTCGCCCCCTGCAGA
TCGATGACGATTTCTGCGGGCAGGACTTCAACAGCCCCCTGGGGGACAGTCAACATTGAGGGGACGCCCCCTGTTCTGTG
GACAAGGATGATGGCTGACCGCGTGGCTGCTATGACTATCGGGGCGCACTGTGTTATTCGCCGGCACGCGAAGTGG
CCGATCCGCAAGATCTGTGTGACCTCTCAACCCCGGTGGCGGGCCTGCCCTGGCCTACGAGAGCGTCTGTGGCCACAG
AGGGCAGCCCCATCCTGCGAGACCTCGTCTCAGCCCCAACCAAGTACCTTACGCCATGACCGAGAAGCAGGTGACG
CGGTGCTGTGGAGAGCTGTGTGACGACGCTCTGTGAGCTGTGTCTGGGGTACGGGACCCCCACTGTGGCTGGTG
TGTCTGCACAGCATGTGCTCGCGGCGGACGCTGTGAGCGAGCAGACGAGCCCCAGCGCTTTGTGCGGACCTGTGTC
AGTGTGTGACGCTGACTGTGACGCCCGCAATGTGTCTGTCAACATGTCCCAGGTCCCAGTACTTGTGCTGACGGCCTGG
AACGTGCCTGACCTCTCAGCTGGCGTCAACTGCTCCTTCGAGGACTTACCGGAATCTGAGAGCGTCTGGAGGATGGCCG
GATCCACTGCCGCTCACCTTCCGCCCGGAGGTGGCGCCCATCACGCGGGGCCAGGGTGAGGGAGACAGCGGGTGGTGA
AACTCTACCTAAAGTCAAGGAGACAGGGAAGAAGTTTGGCTGTGTGGAATCTGCTCTTCACTGACGCGTCCACAG
TCGAGCTGCCTGTCTGTGTCAACGGCTCCTTTCCCTGCCACTGGTGCAAAATACCGCCACGTTGTGCACACAACTGGC
TGACTGCGCCTTCTGGAGGGCGGTGTCAACGTGTCTGAGGACTGCCACAGATCCTGCCCTCCACGAGATCTACGTGC
CAGTGGGAGTGGTAAACCCATCACCTTGGCCGACGGAACCTGCCACAGCCACAGTCAAGGCCAGCGTGGATATGAGTGC
CTCTTCCACATCCCGGGCAGCCCGGCCGTGTACCGCCCTGCGCTTCAACAGCTCCAGCCTGAGTGCCAGAATCTCTC
GTACTCTACGAGGGGAACGATGTGACGACCTGCCAGTGAACCTGTGAGTGTGTGGAACGGCACTTTGTCTATTGACA
ACCCACAGAAATCCAGGCGACCTCTACAAGTCCCCGGCCCTGCGCGAGAGCTGCGGCCTCTGCCTCAAGCCGACCCG
CGCTTCGAGTGGGATGGTGGTGGCGAGCGCGCTGTCCCTGCGACCACTGCGCTGCCGACACACCTGCATCGTG
GATGCACGCGGTGACGCGAGCTGCTGACCGACCCCAAGATCCTCAAGCTGTCCCCGAGACGGGCCGAGGCGAG
GCGGCACGCGGCTCACTATCACAGGCGAGAACCTGGGCTGCGATTCGAAGACGTGCGTCTGGGCGTGGCGTGGGCAAG
GTGCTGTGAGCCCTGTGGAGAGCGAGTACATCAGTGGGAGCAGATCGTCTGTGAGATCGGGGACGCCAGCTCCGTGCG
TGCCCATGACGCCCTGGTGGAGGTGTGTGTGCGGAGTGTCTACCACTACCGCGCCCTGTCAACCAAGCGCTTCACTT

TCGTGACACCAACCTTCTACCGTGTGAGCCCTCCCGTGGGCCTCTGTGACGGGGGCACTGGATTGGCATCGAGGGAAGC
CACCTGAAACGCAGGCAGTGATGTGGCTGTGTCCGTTCGGTGGCCGCGCCCTGCTCTCTTCTCCTGGTCCAGGAGGAACTCCCG
TGAGATCCGGTGCTGACACCCCGGGCAGAGCCCTGGCAGCCTCCCATCATCATCAACATCAACCGCCGCCAGCTCA
CCAACCTTGAGGTGAAGTAGTACAACATCACCGAGAGCCCACTGCTGAGATCGAACCCAGTGGAGATCAACACGCGGT
GGGACCTCCTGACGGTGACAGGCACCAACCTGGCCACTGTCCGTGAACCCCGAATCCGGGCCAAGTATGGAGGCAATTGA
GAGGGAGAACTGCCTGGTGTACAAATGACACCACTGATGTATCCGCGCCGCCGTCTGTGGGCCAACCTGTGCGCAGCCCA
CAGAGCTGGGGGAGCGGCCGATGAGCTGGGCTTCGTATGGACAACGTGCGCTCCCTGCTGTGTCTCAACTCCACCTCC
TTCCTCTACTACCTGACCCCGTACTGGAGCCACTAGCCCCACTGGCCCTGTGGAGCTGAAGCCGAGCTCCCCACTCAT
CCTCAAGGGCCGGAACCTCTGTGCCACTGCAACCGGCACCTCCGACTCAACTACACGGTGTCTCATCGGCTCCACACCCT
GTACCTTCAACCGTGTGGAGACGCAACTGCTGTGGAGGCGCCCAACTCATGGGCAGCAACAGGTGACACGGTTCGTGCA
GGTGGCTTCGAGTTCTCGCCAGGGACACTGCAGGTGTACTCGGACAGCCTGCTGACGCTGCCCTGCCATTGTGGGCATTGG
CGGAGGCGGGGCTCTCCTGCTGCTGGTTCATCGTGGCTGTGCTCATCGCTTACAAGCGCAAGTACAGAGATGCTGACCGCA
CACTCAACGCGGCTGCAGCTCCAGATGGAGCAACCTGGAGTCCCGCGTGGCCCTCGAATGCAAGGAAGCCTTTGCAGAGCTG
CAGACAGACATCCACGAGCTGACCAATGACACTGGAGCGGTGCGGCATCCCTTCTTGTCACTACCGGCATATGCCATGCG
GGTGTCTTTTCTGGGATCGAGGACCAACCTGTGCTCAAGGATGGAGGTACAGGCCAATGTGGAAGTCTGTGACAC
TGTTCCGGCAGCTGCTGACCAAGAAGCACTTCTGTGACCTTCAATCCGCACGCTGGAGGACAGCGCAGCTTCTCCATG
CGCAGCCGCGGGAATGTGCGCTCGCTCATCATGACCGCCCTGACGGGCGAGATGGAATACGCCACAGGCGTGTCTAAGCA
GCTGCTTTCCGAGCTCATCGAGAAGAACCTGGAGAGCAAGAACCAACCCCAAGTCTGCTGCGCGGCCAATGAGTCCG
TGGCAGAGAAGATGCTAACTAAGTTCCTCTTGTATAAGTTCTCAAGGAGTGCCTGGGGAGCGCGTGTCT
ATGCTGTACTCGGCCCATCAAGCAGCAGATGGAGAAGGGCCCAATTGACGCCATCACGGTGAGGCACGCTACTCCCTGAG
TGAGGACAAGCTCATCCGCGCAGATGTGACTACAAGACATGACCTGAACTGTGTGAACCTGAGAATGAGAATGAC
TCTGAGTGGCCGTGTAAGGGGCTGACTGTGACACGCTACCCAGGCCAAGGAGAAGCTGTGACGCTGCTTACAAGGGC
GTGCCCTACTCCCAGCGGCCAACGGCCGCGGACATGGACCTGGAGTGGCGCAGGGCCGATGGCGGCATCATCTTGCA
GGACAGGACGCTGACACCAAGATTGACAACGATTTGAAGAGGCTGAACAACATGCTCTACTACAGGTGACAGACGGGT
CCTCGGTGGCATGTTGGCCCAAGCAGCTGCCCTTACAACATCTCCAACCTTCCACAGCTCCCTCAGCAGAG
TACGAGAGCATGCTCGCAGCGGCAGCAGCCCGCAGACCTGCGCTCGCGCAGCGCCATGATCACGCGCCAGCTTGAGAG
CGGCACAAGCTGTGGCACCTGGTGAAGAACACGACCACTGGACCAGCGTGAGGGTGACCGCGGCAGCAAGATGGTCT
CGGAGATCTACTTGACACGGCTACTGGCCACCAAGCAGGGCAGCTGACAGATTTTGTGACGAGTGTGTTGACCAATC
TTCAGCAGCGGCACCGGGGCTCAGCCCTGCCGCTGGCCATCAAGTACATGTTTCGATCTCTCTGATGAGCAGGCGGACAA
GCACCAGATCCACGATGCTGACGTGCGCCACACTTGAAGAGCAACTGACGCTTGCCTTCTGGTGTGAACGTGA
TCAAGAACCCACAGTTTGTGTTTCGACATCAACAAGAACAGCATACGGAACGCTGCTTGTGCGTGGTGGCCAGACCTTC
ATGACTCTCTGCTCCACCTCTGAGCAACAGTGGGCAAGGACTACCTTCCAAACAGCTGCTCTACGCCAAGGACATCCC
CAACTACAAGAGCTGGGTGGAGAGGAGGTACTATGCAGACATGCGCAAGATGCGACCATCAGCAGCAGGACATGAGTG
CGTATCTGGCTGAGCAGTCCCGCTGCACCTGAGCCAGTTCAACAGCATGAGCGCCTTGACAGCATGCTACTCTACATC
ACCAAGTACAAGGATGAGGTGCAGATCCTGGCAGCCTTGAGGAAGGATGAGCAGGCGCGGCGGACGCGGTGCGGAGCAA
GCTGGAGCAGGTGGTGGACAGCATGCCCCTGAGCAGCTGAGCCCAAGCTGTGATCATCCAGCATGATGACGCGTGAGGAC
AGCTGAGCAGGACCGGGACAGCCCTACCGCATGCGTGTGGAGTGTCCGGTGGT

In a search of public sequence databases, the NOV12 nucleic acid sequence, located on chromosome 8 has 2950 of 3362 bases (87%) identical to a plexin-1 mRNA from *Mus musculus*, (GENBANK-ID: D86948) (E = 0.0). Public nucleotide databases include all

5 GenBank databases and the GeneSeq patent database.

The disclosed NOV12 polypeptide (SEQ ID NO:32) encoded by SEQ ID NO:31 has 1925 amino acid residues and is presented in Table 12B using the one-letter amino acid code. Signal P, Psort and/or Hydropathy results predict that NOV12 contains a signal peptide and is likely to be localized in the plasma membrane with a certainty of 0.6000. In other
10 embodiments, NOV12 is likely to be localized to the Golgi body with a certainty of 0.4000, to the endoplasmic reticulum (membrane) with a certainty of 0.1000, or to the endoplasmic reticulum (lumen) with a certainty of 0.1000. The most likely cleavage site for NOV12 is between positions 44 and 45: MWA-EA.

Table 12B. Encoded NOV12 protein sequence (SEQ ID NO:32).

MMLTPAGPEHRGPRPQPAMPLPPRSLQVLLLLLLLLLLLLPGMWAEAGLPRAGGGSOPPFRTFSASDWGLTHL

VVHEQTGEVYVGAVNRIYKLSGNLTLLRAHVTGPVEDNEKCYPPPSVQSCPHGLGSTDNVNKL LLLLDYAANR
 LLACGSASQGIQFLRLDDLFLKLGEPHHRKEHYLSSVQEAGSMAGVLIAGPPGQQAFLVGTPIIDGKSEYF
 PTLSSRRLLMANEEDADMFGFVYQDEFVSSQLKIPSDTLKSPAFDIYVYSFRSEQFVYYLTQLDTQLTSP
 DAAGEHFFTSKIVRLCVDDPKFYSYVEFFIGCEQAGVEYRLVQDAYLSRPGRALAHQLGLAEDEDVLFVFA
 QGQKNRVKPPKESALCLFTLRAIKEKIKERIQSCYRGEGKLSLPWLLNKELGCINSPLQIDDDFCGQDFNQF
 LGGTVTIEGTPLEFVDKDDGLTAVAAIDYRGRTVVFAGTRSGRIRKILVDLSNPGGRPALAYESVVAQEGSPI
 LRDVLVSPNHQYLYAMTEKQVTRVPVESCQYTSCELCGSRDPHCGWCVLHSMCSRRDACERADEPQRFAD
 DLLQCVQLTVQPRNVSVTMSQVPVLVLQAWNVPDLSAGVNCSEDFTESESVLEDGRIHCRSPSAREVAPIT
 RGQGEQDQVRVVKLYLKSKEGKGFASVDFVFNCSVHQSSCLSCVNGSFPCHWCKYRHVCTHNVDCAFLEG
 RVNVEDCPQILPSTQIYVPGVVKPITLAARNLPQPQSGQRGYECLEFHIPGSPARVTALRFNSSLQCNQNS
 SYSYEGNDVSDLPVNLSVWNGNFVIDNPQNIQAHLYKCPALRESCGLCLKADPRFECGWCVAERRCSLRHH
 CAADTPASWMHARHGSSRCTDPKILKLSPETGPRQGGRTRLTITGENLGLRFEDVRLGVRVGKVLCSPESEY
 ISAEQIVCEIGDASSVRAHDALVEVCVRDCSPHYRALSPKRFTFVTPTFYRVSPSRGPLSGGTWIGEGSHL
 NAGSDVAVSVGGRPCSFSWSRRNSREIRCLTPPGQSPGSAPIIININRAQLTNPEVKYNYTEDPTILRIDPE
 WSINSGGTLTGTGTNLATVREPRIRAKYGGIERENCLVYNDTTMVCRAPSVANPVRSPPELGERDELDGFEV
 MDNVRSLVNSTSFLYYPDPVLEPLSPTGLLELKPSPLILKGRNLLPPAGNSRLNYTVLIGISTPCTLT
 SETQLLCEAPNLTGQHKVTVRAGGFESPGTLQVYSDSLTLPAIVGIGGGGGLLLVIAVLIAYKRKSRD
 ADRTLKRLQLQMDNLESRALECKEFAELQTDIHELTDNDGAGIPFLDYRTYAMRVLFPGIEDHPVLKEM
 EVQANVEKSLTLFGQLLTKKHFLTLFIRTEAQRFSFMRDRGNVASLIMTALQGEMEYATGVKQLLSDLIE
 KNLESKNHPKLLLRPTESVAEKMLTNWFTFLLYKFLKECAGEPLFMYCAIKQMEKGPIDAITGEARSL
 SEDKLIRQIDYKTLTLCVNPENENAEVVPVKGLEDCTVTQAKEKLLDAAYKGVPSYRQPKAADMLEWRQ
 GRMARIILQDEDTVTKIDNDWKRLNLTALHYQVTDGSSVALVPKQTSAYNISNSSTFTKLSRYESMLRTAS
 PDSLRSRTPMITPDLESGTKLWHLVKNHDLQREGDRGSKMVSEIYLRLATKQGTQLKQFVDDLFTETIFS
 TAHRGSALPLAIKYMFDLDEQADKHQIHDADVRHTWKSNCSLPLRFVWVNIKNPQFVFDIHKNSITDCL
 VVAQTFMDCSCTSEHKLKGDSPSNKLYAKDIPNYKSWVERRYYADIAKMPAISDQMSAYLAEQSRHLHSQ
 FNSMSALHEIYSYITKYKDEVQILAALEKDEQARRQLRLSKLEQVVDTMALSS

A search of sequence databases reveals that the NOV12 amino acid sequence has 1820
 of 1907 amino acid residues (95%) identical to, and 1859 of 1907 amino acid residues (97%)
 similar to, the 1894 amino acid residue plexin-1 protein from *Mus musculus* (P70206) (E =
 5 0.0). Public amino acid databases include the GenBank databases, SwissProt, PDB and PIR.

NOV12 is expressed in at least the following tissues: whole organism, brain, testis,
 trabecular Bone, lymph, germinal center B cells. In addition, NOV12 is predicted to be
 expressed in the following tissues because of the expression pattern of (GENBANK-ID:
 acc:AI255192) a closely related plexin-1 homolog in species *Mus musculus*: brain, testis.

10 The disclosed NOV12 polypeptide has homology to the amino acid sequences shown
 in the BLASTP data listed in Table 12C.

Table 12C. BLAST results for NOV12					
Gene Index/ Identifier	Protein/ Organism	Length (aa)	Identity (%)	Positives (%)	Expect
Ptnr:SPTREMBL- ACC:P70206	PLEXIN 1 - Mus musculus	1894	1820/1907 (95%)	1859/1907 (97%)	0.0
ptnr:SPTREMBL- ACC:Q9UIW2	NOV/PLEXIN-A1 PROTEIN - Homo sapiens	1754	1743/1762 (98%)	1746/1762 (99%)	0.0
ptnr:SPTREMBL- ACC:Q91823	PLEXIN PRECURSOR - Xenopus laevis	1905	1603/1893 (84%)	1730/1893 (91%)	0.0
ptnr:SWISSPROT- ACC:P51805	Plexin A3 precursor (Plexin 4)	1871	1252/1874 (66%)	1483/1874 (79%)	0.0

ptnr: SPTREMBL- ACC: P70208	PLEXIN 3 - Mus musculus	1872	1245/1874 (66%)	1478/1874 (78%)	0.0
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The homology between these and other sequences is shown graphically in the ClustalW analysis shown in Table 12D. In the ClustalW alignment of the NOV12 protein, as well as all other ClustalW analyses herein, the black outlined amino acid residues indicate regions of conserved sequence (*i.e.*, regions that may be required to preserve structural or functional properties), whereas non-highlighted amino acid residues are less conserved and can potentially be altered to a much broader extent without altering protein structure or function.

Table 12D. ClustalW Analysis of NOV12

1)	NOV12 (SEQ ID NO:32)	
2)	ptnr: PLEXIN 1 - Mus musculus (SEQ ID NO:81)	
3)	ptnr: NOV/PLEXIN-A1 PROTEIN - Homo sapiens (SEQ ID NO:82)	
4)	ptnr: PLEXIN PRECURSOR - Xenopus laevis (SEQ ID NO:83)	
5)	ptnr: Plexin A3 precursor (Plexin 4) (SEQ ID NO:84)	
6)		
NOV12	MMLTTPAGPEHRRGPRQPAMPYPPRSLOVLLLLLLYLLIPGMABAGLPRAGGSGPPPTFFSASDWGLTHLVVHEQTGE	80
P70206	-----PLPPLSSRTLLLLLLLRGVMTISSPFAGLCPQAFRTFFVASDWGLTHLVVHEQTGE	60
Q9UIW2	-----CMABAGLPRAGGSGPPPTFFSASDWGLTHLVVHEQTGE	40
Q91823	-----LLHAERPLPFHNTFVILCSMTIT-----GCGSPKLPRTFAGSDGLTHLVVHNTGE	55
P51805	-----NPSVGLLLFLAVG-----CALGNRPFRAGVVTDTLTHLAVHRTGE	44
NOV12	VYVGAVNRIYKLSGNLTLLRAHVTGPVEDNEKCYPPPSVQSCPHGLGSTDNNKLLLLDYAANRLACGSASQGICQFLR	160
P70206	VYVGAVNRIYKLSGNLTLLRAHVTGPVEDNEKCYPPPSVQSCPHGLGSTDNNKLLLLDYAANRLACGSASQGICQFLR	140
Q9UIW2	VYVGAVNRIYKLSGNLTLLRAHVTGPVEDNEKCYPPPSVQSCPHGLGSTDNNKLLLLDYAANRLACGSASQGICQFLR	120
Q91823	VYVGAVNRIYKLSGNLTLLRAHVTGPVEDNEKCYPPPSVQSCPHGLGSTDNNKLLLLDYAANRLACGSASQGICQFLR	135
P51805	VYVGAVNRIYKLSGNLTLLRAHVTGPVEDNARCYPPPSRVCAHRLAPVDNINKLLLDYAARRLVACGSITWGICQFLR	124
NOV12	LDLFLKLGEPHHRKEHYLSSVOEAGSMAGVLIAGPPGQGOAKLFVGTPIDGKSEYFPTLSSRRLMANEEDADMFGFVYQL	240
P70206	LDLFLKLGEPHHRKEHYLSSVOEAGSMAGVLIAGPPGQGOAKLFVGTPIDGKSEYFPTLSSRRLMANEEDADMFGFVYQL	220
Q9UIW2	LDLFLKLGEPHHRKEHYLSSVOEAGSMAGVLIAGPPGQGOAKLFVGTPIDGKSEYFPTLSSRRLMANEEDADMFGFVYQL	200
Q91823	LDLFLKLGEPHHRKEHYLSSVNESG-----	160
P51805	LDLFLKLGEPHHRKEHYLSGAEPTSMAGVIVR--QCQCPSKLFGVTAVDGKSEYFPTLSSRRLTISGDSADMFGFVYQL	202
NOV12	EFVSSOLKIPSDTSLKFPAPDIYVYSFRSEQFVYVLTQLDQTLTSPDAAGEHFFTSKIVRLCVDOPKFYSYVEFFPGC	320
P70206	EFVSSOLKIPSDTSLKFPAPDIYVYSFRSEQFVYVLTQLDQTLTSPDAAGEHFFTSKIVRLCVDOPKFYSYVEFFPGC	300
Q9UIW2	EFVSSOLKIPSDTSLKFPAPDIYVYSFRSEQFVYVLTQLDQTLTSPDAAGEHFFTSKIVRLCVDOPKFYSYVEFFPGC	280
Q91823	-----	160
P51805	EFVSSOLKIPSDTSLKFPAPDIYVYSFRSEQFVYVLTQLDQTLTSPDAAGEHFFTSKIVRLCVDOPKFYSYVEFFPGC	282
NOV12	EQAGVEYRLVQDAYLSRPGRALAHQLGLAEDEDVLFVFAQGOQNRVKPKKESALCLFTLRAIKEKIKERIQSCYRGEGF	400
P70206	EQAGVEYRLVQDAYLSRPGRALAHQLGLAEDEDVLFVFAQGOQNRVKPKKESALCLFTLRAIKEKIKERIQSCYRGEGF	380
Q9UIW2	EQAGVEYRLVQDAYLSRPGRALAHQLGLAEDEDVLFVFAQGOQNRVKPKKESALCLFTLRAIKEKIKERIQSCYRGEGF	360
Q91823	-----	160
P51805	SWREVEYRLVCSAHUAKPGCLLLAQAAGCPADEDEDVLFVFAQGOQNRVKPKKESALCLFTLRAIKEKIKERIQSCYRGEGF	362
NOV12	LSLPWLLNKELGCINSPLQIDDDFCQODFNQPLGGTGTIEGTPLFVDNDGDLTAVAAYDYRGRTVVFAGRSGRIRKILV	480
P70206	LSLPWLLNKELGCINSPLQIDDDFCQODFNQPLGGTGTIEGTPLFVDNDGDLTAVAAYDYGRVTVFAGRSGRIRKILV	460
Q9UIW2	LSLPWLLNKELGCINSPLQIDDDFCQODFNQPLGGTGTIEGTPLFVDNDGDLTAVAAYDYGRVTVFAGRSGRIRKILV	440
Q91823	-----	160
P51805	LSLPWLLNKELFCINTPEQINGNFCGLVLNQLPGGLHVTIEGLPLLAESTDGMASVAAYTVRCHSVVRIETRSGLSKKRYR	442
NOV12	DLNPGGRPALAYESVVAOEGSPILRDLVLSPNHOYLYAMTEKQVTVPVESCVQYTSCELCLSRDPHCGWCVLHSLCS	560
P70206	DLNPGGRPALAYESVVAOEGSPILRDLVLSPNHOYLYAMTEKQVTVPVESCVQYTSCELCLSRDPHCGWCVLHSLCS	540
Q9UIW2	DLNPGGRPALAYESVVAOEGSPILRDLVLSPNHOYLYAMTEKQVTVPVESCVQYTSCELCLSRDPHCGWCVLHSLCS	520
Q91823	-----	160
P51805	DG----FDPAHLVETIPVVVGGSPILRDILFSPDRHYVLSSEKQVSLPVERGEQVSCAACLSGSDPHCGWCVLHRRCC	518
NOV12	RRDACERAEPPORFADLLQCVOLTQVPRNVSVTMSQVFLVLQAWNPDLASAGVNCSPFEDFTESVLE-DGRIHCHSF	639
P70206	RRDACERAEPPORFADLLQCVOLTQVPRNVSVTMSQVFLVLQAWNPDLASAGVNCSPFEDFTESVLE-DGRIHCHSF	618
Q9UIW2	RRDACERAEPPORFADLLQCVOLTQVPRNVSVTMSQVFLVLQAWNPDLASAGVNCSPFEDFTESVLE-DGRIHCHSF	598
Q91823	-----	160
P51805	RRDACERAEPPORFADLLQCVOLTQVPRNVSVTMSQVFLVLQAWNPDLASAGVNCSPFEDFTESVLE-DGRIHCHSF	597
NOV12	SAREVAPITRGCGEGDQRVVKLYLKSKEGKGFASVDFVFNCSVHQSCLSCVNGSFPCHWKYRHVCTHNVADCAFLR	719
P70206	SAREVAPITRGCGEGDQRVVKLYLKSKEGKGFASVDFVFNCSVHQSCLSCVNGSFPCHWKYRHVCTHNVADCAFLR	695

	Q9UIW2	SAREVAPITRGC--GDQRVVKLYKSKETGKKFASVDFVFYVCSVHQS-CLSCVNGSFPCHWCKYRHVCTHNVADCAFLE	675
	Q91823	SLCETRALTRGH--CATRTVRLDQLSKETGVRFAGADVFYVCSVLQS-CLSCVNGSFPCHWCKYRHVCTSRPHSCSFC	160
5	P51805	SLCETRALTRGH--CATRTVRLDQLSKETGVRFAGADVFYVCSVLQS-CLSCVNGSFPCHWCKYRHVCTSRPHSCSFC	674
	NOV12	GRVNVSEDCPQILPSTQIYVPVGVPKPTLAARNLPQPOSQORGYECLFHI PGSPARVITALRFNSSSLQCCNSSSYSECN	799
	P70206	GRVNVSEDCPQILPSTQIYVPVGVPKPTLAARNLPQPOSQORGYECLFHI PGSPARVITALRFNSSSLQCCNSSSYSECN	775
	Q9UIW2	GRVNVSEDCPQILPSTQIYVPVGVPKPTLAARNLPQPOSQORGYECLFHI PGSPARVITALRFNSSSLQCCNSSSYSECN	755
	Q91823	GRVNVSEDCPQILPSTQIYVPVGVPKPTLAARNLPQPOSQORGYECLFHI PGSPARVITALRFNSSSLQCCNSSSYSECN	160
10	P51805	GRVNVSEDCPQILPSTQIYVPVGVPKPTLAARNLPQPOSQORGYECLFHI PGSPARVITALRFNSSSLQCCNSSSYSECN	754
	NOV12	DVSDLPVNLSSVVMNCFNVIDNPONIQAHLKYCPALRSCGLCLKADPRFECGWCVAERRCSLRHHCAADIPASWMMHARHC	879
	P70206	DVSDLPVNLSSVVMNCFNVIDNPONIQAHLKYCPALRSCGLCLKADPRFECGWCVAERRCSLRHHCAADIPASWMMHARHC	855
	Q9UIW2	DVSDLPVNLSSVVMNCFNVIDNPONIQAHLKYCPALRSCGLCLKADPRFECGWCVAERRCSLRHHCAADIPASWMMHARHC	835
	Q91823	DVSDLPVNLSSVVMNCFNVIDNPONIQAHLKYCPALRSCGLCLKADPRFECGWCVAERRCSLRHHCAADIPASWMMHARHC	160
15	P51805	DVSDLPVNLSSVVMNCFNVIDNPONIQAHLKYCPALRSCGLCLKADPRFECGWCVAERRCSLRHHCAADIPASWMMHARHC	833
	NOV12	SSRCTDPKILKLSPETGPRQGGTRLTITGENLGLRFEDVRLGVIRVGVKVLCSPVSEYISAEQIVCEIGDASSVRAHDALV	959
	P70206	SSRCTDPKILKLSPETGPRQGGTRLTITGENLGLRFEDVRLGVIRVGVKVLCSPVSEYISAEQIVCEIGDASSVRAHDALV	935
	Q9UIW2	SSRCTDPKILKLSPETGPRQGGTRLTITGENLGLRFEDVRLGVIRVGVKVLCSPVSEYISAEQIVCEIGDASSVRAHDALV	915
20	Q91823	SSRCTDPKILKLSPETGPRQGGTRLTITGENLGLRFEDVRLGVIRVGVKVLCSPVSEYISAEQIVCEIGDASSVRAHDALV	160
	P51805	SSRCTDPKILKLSPETGPRQGGTRLTITGENLGLRFEDVRLGVIRVGVKVLCSPVSEYISAEQIVCEIGDASSVRAHDALV	911
	NOV12	EVCVRDCSPHYRALSPPKRFTEVTPTFYRVSPSRGPLSGGTWIGIEGSHLNAGSDVAVSVGGRPCSFWSRRNSREIRCLT	1039
	P70206	EVCVRDCSPHYRALSPPKRFTEVTPTFYRVSPSRGPLSGGTWIGIEGSHLNAGSDVAVSVGGRPCSFWSRRNSREIRCLT	1013
25	Q9UIW2	EVCVRDCSPHYRALSPPKRFTEVTPTFYRVSPSRGPLSGGTWIGIEGSHLNAGSDVAVSVGGRPCSFWSRRNSREIRCLT	993
	Q91823	EVCVRDCSPHYRALSPPKRFTEVTPTFYRVSPSRGPLSGGTWIGIEGSHLNAGSDVAVSVGGRPCSFWSRRNSREIRCLT	160
	P51805	EVCVRDCSPHYRALSPPKRFTEVTPTFYRVSPSRGPLSGGTWIGIEGSHLNAGSDVAVSVGGRPCSFWSRRNSREIRCLT	989
	NOV12	PPGOS-PGSAPITITININRAOLINPEVKYNYTEDPTILRIDPEWSINSGGTLTIVTGTNLATVREPRIRAKYGGIEREN-C	1117
	P70206	PPGOS-PGSAPITITININRAOLINPEVKYNYTEDPTILRIDPEWSINSGGTLTIVTGTNLATVREPRIRAKYGGIEREN-C	1092
	Q9UIW2	PPGOS-PGSAPITITININRAOLINPEVKYNYTEDPTILRIDPEWSINSGGTLTIVTGTNLATVREPRIRAKYGGIEREN-C	1072
	Q91823	PPGOS-PGSAPITITININRAOLINPEVKYNYTEDPTILRIDPEWSINSGGTLTIVTGTNLATVREPRIRAKYGGIEREN-C	160
30	P51805	PPGOS-PGSAPITITININRAOLINPEVKYNYTEDPTILRIDPEWSINSGGTLTIVTGTNLATVREPRIRAKYGGIEREN-C	1069
	NOV12	LVVNDTMMVCRAPSVANFVRSPPELGERPDEIGFVMDNVRSLLVINSISFLYYPDPVLEPLSPTGLLELKPSPLILKGF	1197
	P70206	LVVNDTMMVCRAPSVANFVRSPPELGERPDEIGFVMDNVRSLLVINSISFLYYPDPVLEPLSPTGLLELKPSPLILKGF	1172
	Q9UIW2	LVVNDTMMVCRAPSVANFVRSPPELGERPDEIGFVMDNVRSLLVINSISFLYYPDPVLEPLSPTGLLELKPSPLILKGF	1152
	Q91823	LVVNDTMMVCRAPSVANFVRSPPELGERPDEIGFVMDNVRSLLVINSISFLYYPDPVLEPLSPTGLLELKPSPLILKGF	160
40	P51805	LVVNDTMMVCRAPSVANFVRSPPELGERPDEIGFVMDNVRSLLVINSISFLYYPDPVLEPLSPTGLLELKPSPLILKGF	1149
	NOV12	NLLPPAPGNSRINYTVLIGSTPCILTVSETOLLCEAPNLTGQHKVTVRAGGFESPGTLQVYSDSLTLTPAIVIGIGGGGG	1277
	P70206	NLLPPAPGNSRINYTVLIGSTPCILTVSETOLLCEAPNLTGQHKVTVRAGGFESPGTLQVYSDSLTLTPAIVIGIGGGGG	1252
	Q9UIW2	NLLPPAPGNSRINYTVLIGSTPCILTVSETOLLCEAPNLTGQHKVTVRAGGFESPGTLQVYSDSLTLTPAIVIGIGGGGG	1232
	Q91823	NLLPPAPGNSRINYTVLIGSTPCILTVSETOLLCEAPNLTGQHKVTVRAGGFESPGTLQVYSDSLTLTPAIVIGIGGGGG	160
45	P51805	NLLPPAPGNSRINYTVLIGSTPCILTVSETOLLCEAPNLTGQHKVTVRAGGFESPGTLQVYSDSLTLTPAIVIGIGGGGG	1229
	NOV12	LLLLIVAVLIAVYKRRSRDADRTLKRLQLOMDNLESVALECKEAFABELOTDIHELTDLDGAGIPFLDYRTYAMRVLFF	1357
	P70206	LLLLIVAVLIAVYKRRSRDADRTLKRLQLOMDNLESVALECKEAFABELOTDIHELTDLDGAGIPFLDYRTYAMRVLFF	1332
	Q9UIW2	LLLLIVAVLIAVYKRRSRDADRTLKRLQLOMDNLESVALECKEAFABELOTDIHELTDLDGAGIPFLDYRTYAMRVLFF	1312
50	Q91823	LLLLIVAVLIAVYKRRSRDADRTLKRLQLOMDNLESVALECKEAFABELOTDIHELTDLDGAGIPFLDYRTYAMRVLFF	160
	P51805	LLLLIVAVLIAVYKRRSRDADRTLKRLQLOMDNLESVALECKEAFABELOTDIHELTDLDGAGIPFLDYRTYAMRVLFF	1309
	NOV12	GIEDHPVLKEMEVOANVEKSLTLFGQLLTKKHFLFTFIRTLAQRSFSMRDRGNVASLIMTALQGEYATGVLKQLLSE	1437
	P70206	GIEDHPVLKEMEVOANVEKSLTLFGQLLTKKHFLFTFIRTLAQRSFSMRDRGNVASLIMTALQGEYATGVLKQLLSE	1412
55	Q9UIW2	GIEDHPVLKEMEVOANVEKSLTLFGQLLTKKHFLFTFIRTLAQRSFSMRDRGNVASLIMTALQGEYATGVLKQLLSE	1392
	Q91823	GIEDHPVLKEMEVOANVEKSLTLFGQLLTKKHFLFTFIRTLAQRSFSMRDRGNVASLIMTALQGEYATGVLKQLLSE	160
	P51805	GIEDHPVLKEMEVOANVEKSLTLFGQLLTKKHFLFTFIRTLAQRSFSMRDRGNVASLIMTALQGEYATGVLKQLLSE	1389
	NOV12	LIEKNLESNNHPKLLLRRTESVAEKMLTNWFTFLLYKFLKECAGEPLFMYCAIKOOMEKGPIDAITGEARYSLSEDKI	1517
	P70206	LIEKNLESNNHPKLLLRRTESVAEKMLTNWFTFLLYKFLKECAGEPLFMYCAIKOOMEKGPIDAITGEARYSLSEDKI	1491
	Q9UIW2	LIEKNLESNNHPKLLLRRTESVAEKMLTNWFTFLLYKFLKECAGEPLFMYCAIKOOMEKGPIDAITGEARYSLSEDKI	1471
	Q91823	LIEKNLESNNHPKLLLRRTESVAEKMLTNWFTFLLYKFLKECAGEPLFMYCAIKOOMEKGPIDAITGEARYSLSEDKI	160
60	P51805	LIEKNLESNNHPKLLLRRTESVAEKMLTNWFTFLLYKFLKECAGEPLFMYCAIKOOMEKGPIDAITGEARYSLSEDKI	1468
	NOV12	IRQOIDYKTLTLNVCNPEBNAPEVPVKGLDCDVTVOAKEKLLDAVYKGVPSORPKAEDMDLEWROGRMARIILQDEDV	1597
	P70206	IRQOIDYKTLTLNVCNPEBNAPEVPVKGLDCDVTVOAKEKLLDAVYKGVPSORPKAEDMDLEWROGRMARIILQDEDV	1571
	Q9UIW2	IRQOIDYKTLTLNVCNPEBNAPEVPVKGLDCDVTVOAKEKLLDAVYKGVPSORPKAEDMDLEWROGRMARIILQDEDV	1551
	Q91823	IRQOIDYKTLTLNVCNPEBNAPEVPVKGLDCDVTVOAKEKLLDAVYKGVPSORPKAEDMDLEWROGRMARIILQDEDV	160
70	P51805	IRQOIDYKTLTLNVCNPEBNAPEVPVKGLDCDVTVOAKEKLLDAVYKGVPSORPKAEDMDLEWROGRMARIILQDEDV	1548
	NOV12	ITKIDNDWKRLNLTAHQVTDGSSVALVPKQTSAYNISNSSTFTKLSRYESMLRTASSPDSLRSRTPMITPDLESCTKL	1677
	P70206	ITKIDNDWKRLNLTAHQVTDGSSVALVPKQTSAYNISNSSTFTKLSRYESMLRTASSPDSLRSRTPMITPDLESCTKL	1651
	Q9UIW2	ITKIDNDWKRLNLTAHQVTDGSSVALVPKQTSAYNISNSSTFTKLSRYESMLRTASSPDSLRSRTPMITPDLESCTKL	1631
	Q91823	ITKIDNDWKRLNLTAHQVTDGSSVALVPKQTSAYNISNSSTFTKLSRYESMLRTASSPDSLRSRTPMITPDLESCTKL	160
75	P51805	ITKIDNDWKRLNLTAHQVTDGSSVALVPKQTSAYNISNSSTFTKLSRYESMLRTASSPDSLRSRTPMITPDLESCTKL	1628
	NOV12	WHLVKNHDLDOREGDRGSKMVSEIYLTRLLATKCTLOKFVDDLFETIFSTAHRGSALPLAIKYMFDPLDEQADKHQIH	1757
	P70206	WHLVKNHDLDOREGDRGSKMVSEIYLTRLLATKCTLOKFVDDLFETIFSTAHRGSALPLAIKYMFDPLDEQADKHQIH	1730
	Q9UIW2	WHLVKNHDLDOREGDRGSKMVSEIYLTRLLATKCTLOKFVDDLFETIFSTAHRGSALPLAIKYMFDPLDEQADKHQIH	1710
80	Q91823	WHLVKNHDLDOREGDRGSKMVSEIYLTRLLATKCTLOKFVDDLFETIFSTAHRGSALPLAIKYMFDPLDEQADKHQIH	160
	P51805	WHLVKNHDLDOREGDRGSKMVSEIYLTRLLATKCTLOKFVDDLFETIFSTAHRGSALPLAIKYMFDPLDEQADKHQIH	1707
	NOV12	DADVHTWKSNG-LPLRFVWVNIKNPQFVFDIHKNSITDACLSVVAQTFMDSCTSEHGLGKDSPSNKLKYAKDIPNYKS	1837
	P70206	DADVHTWKSNG-LPLRFVWVNIKNPQFVFDIHKNSITDACLSVVAQTFMDSCTSEHGLGKDSPSNKLKYAKDIPNYKS	1809
85	Q9UIW2	DADVHTWKSNG-LPLRFVWVNIKNPQFVFDIHKNSITDACLSVVAQTFMDSCTSEHGLGKDSPSNKLKYAKDIPNYKS	1754
	Q91823	DADVHTWKSNG-LPLRFVWVNIKNPQFVFDIHKNSITDACLSVVAQTFMDSCTSEHGLGKDSPSNKLKYAKDIPNYKS	160
	P51805	DADVHTWKSNG-LPLRFVWVNIKNPQFVFDIHKNSITDACLSVVAQTFMDSCTSEHGLGKDSPSNKLKYAKDIPNYKS	1786
	NOV12	WVERRYADIAMPAISDQMSAYLAOSRLHLSQFNSALHEHTSYHAKYKD--EILVALEKQOARORLRSKLEQV	1917
90	P70206	WVERRYADIAMPAISDQMSAYLAOSRLHLSQFNSALHEHTSYHAKYKD--EILVALEKQOARORLRSKLEQV	1886

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10

```

Q9UIW2 ----- 1754
Q91823 ----- 160
P51805 NVER-YVRDIAKMASISDQDMPAYLVEOSRLHASDSVLSADNGELTFYVTKYRQ--EITITADREASCRKHKLKLEQ 1863

NOV12 VDTMALSS 1925
P70206 VDTMALSS 1894
Q9UIW2 ----- 1754
Q91823 ----- 160
P51805 RSLVSSDS 1871
  
```

Tables 12E-12N list the domain descriptions from DOMAIN analysis results against NOV12. This indicates that the NOV12 sequence has properties similar to those of other proteins known to contain this domain.

Table 12E. Domain Analysis of NOV12

gnl|Smart|smart00630, Sema, semaphorin domain (SEQ ID NO:113)
 CD-Length = 430 residues, 100.0% aligned
 Score = 242 bits (618), Expect = 1e-64

15
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25
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35
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45

```

Query: 69 LTHLVVHEQTGEVYVGAVNRIYKLSGNLTLLRAHVTGPPVEDNEKCYPPPSVQSCPHGLGS 128
      | +|++ | | +||| | +| | | | | | | | | + | |
Sbjct: 1 LQNLLLEDNGTLYVGARNRLYVLSNLISEAEVKTGPVLSSPDCEEC--VSKGKDP-- 56

Query: 129 TDMVNK-LLLLDYAANRLLAGCS-ASQGICQFLRLDDLFLKGEPHHRKEHYLSSVQEAGS 186
      || | | | | | | | + | | | | | | | | | + | | | |
Sbjct: 57 TDCVNFIRLLLDYNADHLLVCGTNAFQPVCRLLNLGNLDRL-EVGRESGRGRCPDPQHN 115

Query: 187 MAGVLIAGPPGQQAFLVGTPIID--GKSEYFPTLSSRRLMANEEDADMFGFVYQDEFVS 244
      || + | | | | +| +| | | | | | | | | | + |
Sbjct: 116 STAVLVDG-----ELYVGTVAADFSGSDPAIYRSLSVRRLKGTSG-----PSLRTVL 161

Query: 245 SQLKIPSDTLKFPAPFDIYVYSFRSEQFVYVLTQLDQLTSPDAAGEHFFTSKIVRLC 304
      + + + + + + +| +| | | + + + | | | | | | +|
Sbjct: 162 YDSRWLN-----EPNFVYAFESGDFVYF----FFRETAVEDENCGKAVVSRVARVC 208

Query: 305 VDD-----PKFYSYVEFPIGC---EQAGVEYRLVQDAYLSRPGRALAHQLGLAEDED 353
      + | | | | +| +| +| +| +| +| +| +| +| +|
Sbjct: 209 KNDVGGPRSLSKKWTSLKARLECSVPGEFPFYFNLQAAFLLPAG-----SESDD 259

Query: 354 VLFTVFAQGQKNRVKPPKESALCLFTLRAIKEIKERIQSCYRGEGKLSL----PWLLNK 409
      || + || + | | | +| +| | | | | + | | | + |
Sbjct: 260 VLYGVFSTS----SNPIPGSAVCAFSLSDNNAVFNPEPFKECETGNSQWLPYPRGLVPFPR 315

Query: 410 ELGCINSPLQI----DDDFC-GQDFNQPLGGTVTIEGTPLFV--DKDDGLTAVAA----Y 458
      | | +| | | | | + | | | | | | | + | | +|
Sbjct: 316 PGTCNPNTPLSSKDLPPDVLNFIKTHPLMDEVVQPLTGRPLFVKTDNSNYLLTSIAVDRVRT 375

Query: 459 DYRGRTVVFAGRTRSGRIRKILVDLSNPGGRPALAYESVVAQEGSPILRDLVLSPNH 514
      | | | +| | | | | +| +| +| +| +| +| +| +|
Sbjct: 376 DGGNYTVLFLGTSDGRILKVVLSRSSSSSVVLEEISVFDPGSPV-SDLVLSPPK 430
  
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Table 12F. Domain Analysis of NOV12

gnl|Pfam|pfam01403, Sema, Sema domain. The Sema domain occurs in semaphorins, which are a large family of secreted and transmembrane proteins, some of which function as repellent signals during axon guidance. Sema domains also occur in the hepatocyte growth factor receptor. (SEQ ID NO:114)
 CD-Length = 433 residues, 99.5% aligned
 Score = 171 bits (432), Expect = 5e-43

5	Query:	69	LTHLVVHEQTGEVYVGAVNRIYKLSGN----LTLRAHVTGPVEDNEKCYPPPSVQSCPH	124
	Sbjct:	1	FVTLLLEDRGRLYVGARNRVYVLNLEDLSEVLNLKTGWPGSCETCEEKNMGKSP----	56
10	Query:	125	GLGSTDNVN-KLLLLDYAANRLLAGGS-ASQGICQFLRLDDLFLKLGEPHHRKEHYLSSVQ	182
	Sbjct:	57	---LTECTNFIRVLQAYNDTHLYVCGTNAFQPVCTLINLGLDLSLDVDNEEDGCGDCPYD	113
15	Query:	183	EAGSMAGVLIAGPPGQQAFLFVGTPIDGKSEYFPTLSSRRRLMANEEDADMFGFVYQDEF	242
	Sbjct:	114	PLGNTTSVLVQG-----GELYSGTVID-----FSGRDPISIRLLGSHDGLRTEFHD--	159
20	Query:	243	VSSQLKIPSDTLSKFPAFDIYVVSFRSEQFVYYLTLQLDTQLTSPDAAGEHFFTSKIVR	302
	Sbjct:	160	-SKWLNLPNFVD---SYPIHYVHSF-SDDKVYF---FFRETAVEDSNCKTIH-SRVAR	208
25	Query:	303	LCVDDPKFYSYVEFPIGC-----EQAGVEYRLVQDAYLSRPGRALAHQLGLA	349
	Sbjct:	209	VCKNDPGGRSYLELNKWTTFKARLNCSIPGEGTPFYFNELQAAFVLPTG-----A	259
30	Query:	350	EDEDVLFTVFAQQQKNRVKPKESALCLFTLRRAIKE--KIKERIQSCYRGEGKLSLPWLL	407
	Sbjct:	260	DTDPVLYGVFTTS----SNSSAGSAVCAFSMSDINQVFEGPFKHQSPNSKWLPYRGKVPQ	315
35	Query:	408	NKELGCINSP-LQIDDDFCGQDFNQPLGGTVT--IEGTPLFVDKDDG--LTAVA-----A	457
	Sbjct:	316	PRPGQCPNASGLNLPDDTLNFIRCHPLMDEVVPLHNVPLFVGQSGNYRLTSIAVDRVRA	375
40	Query:	458	YDYRGRTVVFAGTRSGRIRKILVDLSNPGGR---PALAYESVVAQEGSPILRDLVLS	511
	Sbjct:	376	GDGQIYTVLFLGTDDGRV-LKQVVLRSSSASYLVVVLEESLVFPDGEVPQRMVISS	431

Table 12G. Domain Analysis of NOV12

gnl|Pfam|pfam01833, TIG, IPT/TIG domain. This family consists of a domain that has an immunoglobulin like fold. These domains are found in cell surface receptors such as Met and Ron as well as in intracellular transcription factors where it is involved in DNA binding. (SEQ ID NO:115)
 CD-Length = 85 residues, 100.0% aligned
 Score = 78.2 bits (191), Expect = 4e-15

35	Query:	983	PTFYRVSPSRGPLSGGTWIGIEGSHLNAAGSDVAVSVGGRPCSFSWSRRNSREIRCLTPPG	1042
	Sbjct:	1	PVITSISPSSGPLSGGTEITITGSLGSGEDIKVTFGGTECDV--VSQEASQIVCKTPPY	58
40	Query:	1043	QSPGSAPIIININRAQLTNPEVKYNYT	1069
	Sbjct:	59	ANGGPQPVTVSLDGGGLSSSPVTFTYV	85

Table 12H. Domain Analysis of NOV12

gnl|Pfam|pfam01833, TIG, IPT/TIG domain. This family consists of a domain that has an immunoglobulin like fold. These domains are found in cell surface receptors such as Met and Ron as well as in intracellular transcription factors where it is involved in DNA binding. (SEQ ID NO:115)
CD-Length = 85 residues, 100.0% aligned
Score = 60.1 bits (144), Expect = 1e-09

5 Query: 886 PKILKLSPETGPRQGGTRLTITGENLGLRFEDVRLGVRVGKVLCSPESEYISAEQIVCE 945
| | + | | + | | | | + | | | | | + | | | | | | | | +
Sbjct: 1 PVITSISPSSGPLSGGTEITITGSNLGS---GEDIKVTFGGTECDVVSQEA---SQIVCK 54
Query: 946 IGDASSVRAHDALVEVCVRDCSPHYRALSPKRFTFV 981
++ | + | | | | + | + |
Sbjct: 55 TPPYANGGPQPVTVSLDGGGLSS-----SPVTFTYV 85

Table 12I. Domain Analysis of NOV12

gnl|Pfam|pfam01833, TIG, IPT/TIG domain. This family consists of a domain that has an immunoglobulin like fold. These domains are found in cell surface receptors such as Met and Ron as well as in intracellular transcription factors where it is involved in DNA binding. (SEQ ID NO:115)
CD-Length = 85 residues, 100.0% aligned
Score = 46.6 bits (109), Expect = 1e-05

10 Query: 1173 PVLEPLSPTGELLEKPSSPLILKGRNLLPPAPGNSRLNYTVLIGSTPCTLT-VSETQLLC 1231
| | + + | | + | + + + | | | + | | | | + + | + |
Sbjct: 1 PVITSISPSSG-PLSGGTEITITGSNL-----GSGEDIKVTFGGTECDVVSQEASQIVC 53
15 Query: 1232 EAPNLTGQH---KVTVRAGGFESPGTLQVY 1259
+ | | | | ++ | | | |
Sbjct: 54 KTPPYANGGPQPVTVSLDGGGLSSSPVTFTYV 85

Table 12J. Domain Analysis of NOV12

gnl|Smart|smart00429, IPT, ig-like, plexins, transcription factors (SEQ ID NO:116)
CD-Length = 93 residues, 100.0% aligned.
Score = 70.9 bits (172), Expect = 6e-13

20 Query: 885 DPKILKLSPETGPRQGGTRLTITGENLGLRFEDVRLGVRVGKVLCSPESEYISAEQIVC 944
| | | ++ | | + | | | | + | + | | + | + | + | | |
Sbjct: 1 DPVITRISPNSGPLSGGTRITLCGKNLDS-ISVVFEVGVGEVPCTFLPSDV-SQTAIVC 58
25 Query: 945 EIGDASSVRAHDALVEVCVRDCSPHYRALSPKRFTFV 981
+ | | | + | | | + |
Sbjct: 59 KTP-PYHNIPGSVPVRVEVGLRNGGVPG-EPSPFTYV 93

Table 12K. Domain Analysis of NOV12

g n l | P f a m | p f a m 0 1 4 3 7 , P l e x i n _ r e p e a t , P l e x i n _ r e p e a t . A c y s t e i n e r i c h
r e p e a t f o u n d i n s e v e r a l d i f f e r e n t e x t r a c e l l u l a r r e c e p t o r s . T h e
f u n c t i o n o f t h e r e p e a t i s u n k n o w n . T h r e e c o p i e s o f t h e r e p e a t a r e
f o u n d P l e x i n . T w o c o p i e s o f t h e r e p e a t a r e f o u n d i n m a h o g a n y p r o t e i n .
A r e l a t e d C . e l e g a n s p r o t e i n c o n t a i n s f o u r c o p i e s o f t h e r e p e a t . T h e
M e t r e c e p t o r c o n t a i n s a s i n g l e c o p y o f t h e r e p e a t . T h e P f a m a l i g n m e n t
s h o w s 6 c o n s e r v e d c y s t e i n e r e s i d u e s t h a t m a y f o r m t h r e e c o n s e r v e d
d i s u l p h i d e b r i d g e s . (S E Q I D N O : 1 1 7)
C D - L e n g t h = 4 8 r e s i d u e s , 1 0 0 . 0 % a l i g n e d
S c o r e = 5 9 . 3 b i t s (1 4 2) , E x p e c t = 2 e - 0 9

Query: 532 SCVQYTSCELCLGSRDPHCGWCVLHSMCSRRDACERADEPQRFAADLLQCV 582
+ | | + | | | | | + | | | | | | + | + | | + + + |
Sbjct: 1 NCSQHTSCGSCLSAPDPGCGWCPSPRKRCRTRLEECR---GEGWSQSQETCP 48

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Table 12L. Domain Analysis of NOV12

g n l | P f a m | p f a m 0 1 4 3 7 , P l e x i n _ r e p e a t , P l e x i n _ r e p e a t . A c y s t e i n e r i c h
r e p e a t f o u n d i n s e v e r a l d i f f e r e n t e x t r a c e l l u l a r r e c e p t o r s . T h e
f u n c t i o n o f t h e r e p e a t i s u n k n o w n . T h r e e c o p i e s o f t h e r e p e a t a r e
f o u n d P l e x i n . T w o c o p i e s o f t h e r e p e a t a r e f o u n d i n m a h o g a n y p r o t e i n .
A r e l a t e d C . e l e g a n s p r o t e i n c o n t a i n s f o u r c o p i e s o f t h e r e p e a t . T h e
M e t r e c e p t o r c o n t a i n s a s i n g l e c o p y o f t h e r e p e a t . T h e P f a m a l i g n m e n t
s h o w s 6 c o n s e r v e d c y s t e i n e r e s i d u e s t h a t m a y f o r m t h r e e c o n s e r v e d
d i s u l p h i d e b r i d g e s . (S E Q I D N O : 1 1 7)
C D - L e n g t h = 4 8 r e s i d u e s , 1 0 0 . 0 % a l i g n e d
S c o r e = 5 3 . 5 b i t s (1 2 7) , E x p e c t = 1 e - 0 7

Query: 681 NCSVHQSSCLSCVNGSFP-CHWCKYRHVCTHNVADCAFLEGRVNVSEDCP 729
| | | | | | | + + | | | | | | + + | | | | |
Sbjct: 1 NCSQHTS-CGSCLSAPDPGCGWCPSPRKRCRTRL-EECSRGEWSQSQETCP 48

10

Table 12M. Domain Analysis of NOV12

g n l | P f a m | p f a m 0 1 4 3 7 , P l e x i n _ r e p e a t , P l e x i n _ r e p e a t . A c y s t e i n e r i c h
r e p e a t f o u n d i n s e v e r a l d i f f e r e n t e x t r a c e l l u l a r r e c e p t o r s . T h e
f u n c t i o n o f t h e r e p e a t i s u n k n o w n . T h r e e c o p i e s o f t h e r e p e a t a r e
f o u n d P l e x i n . T w o c o p i e s o f t h e r e p e a t a r e f o u n d i n m a h o g a n y p r o t e i n .
A r e l a t e d C . e l e g a n s p r o t e i n c o n t a i n s f o u r c o p i e s o f t h e r e p e a t . T h e
M e t r e c e p t o r c o n t a i n s a s i n g l e c o p y o f t h e r e p e a t . T h e P f a m a l i g n m e n t
s h o w s 6 c o n s e r v e d c y s t e i n e r e s i d u e s t h a t m a y f o r m t h r e e c o n s e r v e d
d i s u l p h i d e b r i d g e s . (S E Q I D N O : 1 1 7)
C D - L e n g t h = 4 8 r e s i d u e s , 8 9 . 6 % a l i g n e d
S c o r e = 4 6 . 2 b i t s (1 0 8) , E x p e c t = 2 e - 0 5

Query: 835 RESCGLCLKADPRFECGWCVAERRCSLRHHCAADTPASWMHARHGSSRC 883
| | | | | | | + + | | | + + | +
Sbjct: 5 HTSCGSCLSA-PDPGCGWCPSPRKRCRTRLEEC-----SRGEGWSQSQETC 47

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Table 12N. Domain Analysis of NOV12

gnl|Smart|smart00423, PSI, domain found in Plexins, Semaphorins and Integrins (SEQ ID NO:118)
CD-Length = 47 residues, 89.4% aligned
Score = 44.3 bits (103), Expect = 6e-05

Query: 833 ALRESCGLCLKADPRFECGWCVAERRCSLRHHCAADTPASWMHA 876
+ || || | + || ++ || + | + +
Sbjct: 3 SAYTSCSECLLARDPY-CAWCSSQGRCTSGERCDS-LRQNWSSG 44

5

Plexin is a type I membrane protein which was identified in *Xenopus* nervous system by hybridoma technique. Molecular cloning studies demonstrated that the extracellular segment of the plexin protein possesses three internal repeats of cysteine cluster which are homologous to the cysteine-rich domain of the c-met proto-oncogene protein product. A cell aggregation test revealed that the plexin protein mediated cell adhesion via a homophilic binding mechanism, in the presence of calcium ions. Plexin was expressed in the neuronal elements composing particular neuron circuits in *Xenopus* CNS and PNS. These findings indicate that plexin is a new member of the Ca(2+)-dependent cell adhesion molecules, and suggest that the molecule plays an important role in neuronal cell contact and neuron network formation.

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In the developing nervous system axons navigate with great precision over large distances to reach their target areas. Chemorepulsive signals such as the semaphorins play an essential role in this process. The effects of one of these repulsive cues, semaphorin 3A (Sema3A), are mediated by the membrane protein neuropilin-1 (Npn-1). Recent work has shown that neuropilin-1 is essential but not sufficient to form functional Sema3A receptors and indicates that additional components are required to transduce signals from the cell surface to the cytoskeleton. Members of the plexin family interact with the neuropilins and act as co-receptors for Sema3A. Neuropilin/plexin interaction restricts the binding specificity of neuropilin-1 and allows the receptor complex to discriminate between two different semaphorins. Deletion of the highly conserved cytoplasmic domain of Plexin-A1 or -A2 creates a dominant negative Sema3A receptor that renders sensory axons resistant to the repulsive effects of Sema3A when expressed in sensory ganglia. These data suggest that functional semaphorin receptors contain plexins as signal-transducing and neuropilins as ligand-binding subunits.

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Physiologic SEMA3A receptors consist of NRP1/PLXN1 complexes. Two semaphorin-binding proteins, plexin-1 (PLXN1) and neuropilin-1 (NRP1; 602069), form a

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stable complex. While SEMA3A binding to NRP1 does not alter nonneuronal cell morphology, SEMA3A interaction with NRP1/PLXN1 complexes induces adherent cells to round up. Expression of a dominant-negative PLXN1 in sensory neurons blocked SEMA3A-induced growth cone collapse. SEMA3A treatment led to the redistribution of growth cone NRP1 and PLXN1 into clusters.

The semaphorin family of proteins constitute one of the major cues for axonal guidance. The prototypic member of this family is Sema3A, previously designated semD/III or collapsin-1. Sema3A acts as a diffusible, repulsive guidance cue in vivo for the peripheral projections of embryonic dorsal root ganglion neurons. Sema3A binds with high affinity to neuropilin-1 on growth cone filopodial tips. Although neuropilin-1 is required for Sema3A action, it is incapable of transmitting a Sema3A signal to the growth cone interior. Instead, the Sema3A/neuropilin-1 complex interacts with another transmembrane protein, plexin, on the surface of growth cones. Certain semaphorins, other than Sema3A, can bind directly to plexins. The intracellular domain of plexin is responsible for initiating the signal transduction cascade leading to growth cone collapse, axon repulsion, or growth cone turning. This intracellular cascade involves the monomeric G-protein, Rac1, and a family of neuronal proteins, the CRMPs. Rac1 is likely to be involved in semaphorin-induced rearrangements of the actin cytoskeleton, but how plexin controls Rac1 activity is not known. Vertebrate CRMPs are homologous to the *Caenorhabditis elegans* unc-33 protein, which is required for proper axon morphology in worms. CRMPs are essential for Sema3A-induced, neuropilin-plexin-mediated growth cone collapse, but the molecular interactions of growth cone CRMPs are not well defined. Mechanistic aspects of plexin-based signaling for semaphorin guidance cues may have implications for other axon guidance events and for the basis of growth cone motility.

In *Drosophila*, plexin A is a functional receptor for semaphorin-1a. The human plexin gene family comprises at least nine members in four subfamilies. Plexin-B1 is a receptor for the transmembrane semaphorin Sema4D (CD100), and plexin-C1 is a receptor for the GPI-anchored semaphorin Sema7A (Sema-K1). Secreted (class 3) semaphorins do not bind directly to plexins, but rather plexins associate with neuropilins, coreceptors for these semaphorins. Plexins are widely expressed: in neurons, the expression of a truncated plexin-A1 protein blocks axon repulsion by Sema3A. The cytoplasmic domain of plexins associates with a tyrosine kinase activity. Plexins may also act as ligands mediating repulsion in epithelial cells in vitro. Thus, plexins are receptors for multiple (and perhaps all) classes of semaphorins,

either alone or in combination with neuropilins, and trigger a novel signal transduction pathway controlling cell repulsion.

In addition, recent studies have identified semaphorins and their receptors as putative molecular cues involved in olfactory pathfinding, plasticity and regeneration. The semaphorins
5 comprise a large family of secreted and transmembrane axon guidance proteins, being either repulsive or attractive in nature. Neuropilins were shown to serve as receptors for secreted class 3 semaphorins, whereas members of the plexin family are receptors for class 1 and V (viral) semaphorins.

The disclosed NOV12 nucleic acid of the invention encoding a Plexin-1-like protein
10 includes the nucleic acid whose sequence is provided in Table 12A or a fragment thereof. The invention also includes a mutant or variant nucleic acid any of whose bases may be changed from the corresponding base shown in Table 12A while still encoding a protein that maintains its Plexin-1-like activities and physiological functions, or a fragment of such a nucleic acid. The invention further includes nucleic acids whose sequences are complementary to those just
15 described, including nucleic acid fragments that are complementary to any of the nucleic acids just described. The invention additionally includes nucleic acids or nucleic acid fragments, or complements thereto, whose structures include chemical modifications. Such modifications include, by way of nonlimiting example, modified bases, and nucleic acids whose sugar phosphate backbones are modified or derivatized. These modifications are carried out at least
20 in part to enhance the chemical stability of the modified nucleic acid, such that they may be used, for example, as antisense binding nucleic acids in therapeutic applications in a subject. In the mutant or variant nucleic acids, and their complements, up to about 29 percent of the bases may be so changed.

The disclosed NOV12 protein of the invention includes the Plexin-1-like protein whose
25 sequence is provided in Table 12B. The invention also includes a mutant or variant protein any of whose residues may be changed from the corresponding residue shown in Table 12B, while still encoding a protein that maintains its Plexin-1-like activities and physiological functions, or a functional fragment thereof. In the mutant or variant protein, up to about 29 percent of the residues may be so changed.

30 The protein similarity information, expression pattern, and map location for the plexin-1-like protein and the NOV12 protein disclosed herein suggest that this plexin-1-like protein may have important structural and/or physiological functions characteristic of the mannosidase protein family. Therefore, the nucleic acids and proteins of the invention are useful in potential

The NOV12 nucleic acids and proteins of the invention are useful in potential diagnostic and therapeutic applications implicated in various diseases and disorders described below and/or other pathologies. For example, the compositions of the present invention will have efficacy for treatment of patients suffering from AIDS, cancer therapy, treatment of Neurologic diseases, Brain and/or autoimmune disorders like encephalomyelitis, neurodegenerative disorders, Alzheimer's Disease, Parkinson's Disorder, immune disorders, and hematopoietic disorders, endocrine diseases, muscle disorders, inflammation and wound repair, bacterial, fungal, protozoal and viral infections (particularly infections caused by HIV-1 or HIV-2), pain, cancer (including but not limited to Neoplasm; adenocarcinoma; lymphoma; prostate cancer; uterus cancer), anorexia, bulimia, asthma, Parkinson's disease, acute heart failure, hypotension, hypertension, urinary retention, osteoporosis, Crohn's disease; multiple sclerosis; and Treatment of Albright Hereditary Osteodystrophy, angina pectoris, myocardial infarction, ulcers, asthma, allergies, benign prostatic hypertrophy, and psychotic and neurological disorders, including anxiety, schizophrenia, manic depression, delirium, dementia, severe mental retardation and dyskinesias, such as Huntington's disease or Gilles de la Tourette syndrome, and/or other pathologies/disorders. The NOV12 nucleic acid, or fragments thereof, may further be useful in diagnostic applications, wherein the presence or amount of the nucleic acid or the protein are to be assessed.

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NOVX Nucleic Acids and Polypeptides

One aspect of the invention pertains to isolated nucleic acid molecules that encode NOVX polypeptides or biologically active portions thereof. Also included in the invention are nucleic acid fragments sufficient for use as hybridization probes to identify NOVX-encoding nucleic acids (*e.g.*, NOVX mRNAs) and fragments for use as PCR primers for the amplification and/or mutation of NOVX nucleic acid molecules. As used herein, the term “nucleic acid molecule” is intended to include DNA molecules (*e.g.*, cDNA or genomic DNA), RNA molecules (*e.g.*, mRNA), analogs of the DNA or RNA generated using nucleotide analogs, and derivatives, fragments and homologs thereof. The nucleic acid molecule may be single-stranded or double-stranded, but preferably is comprised double-stranded DNA.

An NOVX nucleic acid can encode a mature NOVX polypeptide. As used herein, a “mature” form of a polypeptide or protein disclosed in the present invention is the product of a naturally occurring polypeptide or precursor form or proprotein. The naturally occurring polypeptide, precursor or proprotein includes, by way of nonlimiting example, the full-length gene product, encoded by the corresponding gene. Alternatively, it may be defined as the polypeptide, precursor or proprotein encoded by an ORF described herein. The product “mature” form arises, again by way of nonlimiting example, as a result of one or more naturally occurring processing steps as they may take place within the cell, or host cell, in which the gene product arises. Examples of such processing steps leading to a “mature” form of a polypeptide or protein include the cleavage of the N-terminal methionine residue encoded by the initiation codon of an ORF, or the proteolytic cleavage of a signal peptide or leader sequence. Thus a mature form arising from a precursor polypeptide or protein that has residues 1 to N, where residue 1 is the N-terminal methionine, would have residues 2 through N remaining after removal of the N-terminal methionine. Alternatively, a mature form arising from a precursor polypeptide or protein having residues 1 to N, in which an N-terminal signal sequence from residue 1 to residue M is cleaved, would have the residues from residue M+1 to residue N remaining. Further as used herein, a “mature” form of a polypeptide or protein may arise from a step of post-translational modification other than a proteolytic cleavage event. Such additional processes include, by way of non-limiting example, glycosylation, myristoylation or phosphorylation. In general, a mature polypeptide or protein may result from the operation of only one of these processes, or a combination of any of them.

The term "probes", as utilized herein, refers to nucleic acid sequences of variable length, preferably between at least about 10 nucleotides (nt), 100 nt, or as many as approximately, *e.g.*, 6,000 nt, depending upon the specific use. Probes are used in the detection of identical, similar, or complementary nucleic acid sequences. Longer length probes are generally obtained from a natural or recombinant source, are highly specific, and much slower to hybridize than shorter-length oligomer probes. Probes may be single- or double-stranded and designed to have specificity in PCR, membrane-based hybridization technologies, or ELISA-like technologies.

The term "isolated" nucleic acid molecule, as utilized herein, is one, which is separated from other nucleic acid molecules which are present in the natural source of the nucleic acid. Preferably, an "isolated" nucleic acid is free of sequences which naturally flank the nucleic acid (*i.e.*, sequences located at the 5'- and 3'-termini of the nucleic acid) in the genomic DNA of the organism from which the nucleic acid is derived. For example, in various embodiments, the isolated NOVX nucleic acid molecules can contain less than about 5 kb, 4 kb, 3 kb, 2 kb, 1 kb, 0.5 kb or 0.1 kb of nucleotide sequences which naturally flank the nucleic acid molecule in genomic DNA of the cell/tissue from which the nucleic acid is derived (*e.g.*, brain, heart, liver, spleen, etc.). Moreover, an "isolated" nucleic acid molecule, such as a cDNA molecule, can be substantially free of other cellular material or culture medium when produced by recombinant techniques, or of chemical precursors or other chemicals when chemically synthesized.

A nucleic acid molecule of the invention, *e.g.*, a nucleic acid molecule having the nucleotide sequence SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, and 217, or a complement of this aforementioned nucleotide sequence, can be isolated using standard molecular biology techniques and the sequence information provided herein. Using all or a portion of the nucleic acid sequence of SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, and 217 as a hybridization probe, NOVX molecules can be isolated using standard hybridization and cloning techniques (*e.g.*, as described in Sambrook, *et al.*, (eds.), MOLECULAR CLONING: A LABORATORY MANUAL 2nd Ed., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, 1989; and Ausubel, *et al.*, (eds.), CURRENT PROTOCOLS IN MOLECULAR BIOLOGY, John Wiley & Sons, New York, NY, 1993.)

A nucleic acid of the invention can be amplified using cDNA, mRNA or alternatively, genomic DNA, as a template and appropriate oligonucleotide primers according to standard PCR amplification techniques. The nucleic acid so amplified can be cloned into an appropriate vector and characterized by DNA sequence analysis. Furthermore,

oligonucleotides corresponding to NOVX nucleotide sequences can be prepared by standard synthetic techniques, *e.g.*, using an automated DNA synthesizer.

As used herein, the term “oligonucleotide” refers to a series of linked nucleotide residues, which oligonucleotide has a sufficient number of nucleotide bases to be used in a PCR reaction. A short oligonucleotide sequence may be based on, or designed from, a genomic or cDNA sequence and is used to amplify, confirm, or reveal the presence of an identical, similar or complementary DNA or RNA in a particular cell or tissue.

Oligonucleotides comprise portions of a nucleic acid sequence having about 10 nt, 50 nt, or 100 nt in length, preferably about 15 nt to 30 nt in length. In one embodiment of the invention, an oligonucleotide comprising a nucleic acid molecule less than 100 nt in length would further comprise at least 6 contiguous nucleotides SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, and 217, or a complement thereof. Oligonucleotides may be chemically synthesized and may also be used as probes.

In another embodiment, an isolated nucleic acid molecule of the invention comprises a nucleic acid molecule that is a complement of the nucleotide sequence shown in SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, and 217, or a portion of this nucleotide sequence (*e.g.*, a fragment that can be used as a probe or primer or a fragment encoding a biologically-active portion of an NOVX polypeptide). A nucleic acid molecule that is complementary to the nucleotide sequence shown SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, or 217 is one that is sufficiently complementary to the nucleotide sequence shown SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, or 217 that it can hydrogen bond with little or no mismatches to the nucleotide sequence shown SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, and 217, thereby forming a stable duplex.

As used herein, the term “complementary” refers to Watson-Crick or Hoogsteen base pairing between nucleotides units of a nucleic acid molecule, and the term “binding” means the physical or chemical interaction between two polypeptides or compounds or associated polypeptides or compounds or combinations thereof. Binding includes ionic, non-ionic, van der Waals, hydrophobic interactions, and the like. A physical interaction can be either direct or indirect. Indirect interactions may be through or due to the effects of another polypeptide or compound. Direct binding refers to interactions that do not take place through, or due to, the effect of another polypeptide or compound, but instead are without other substantial chemical intermediates.

Fragments provided herein are defined as sequences of at least 6 (contiguous) nucleic acids or at least 4 (contiguous) amino acids, a length sufficient to allow for specific hybridization in the case of nucleic acids or for specific recognition of an epitope in the case of amino acids, respectively, and are at most some portion less than a full length sequence.

5 Fragments may be derived from any contiguous portion of a nucleic acid or amino acid sequence of choice. Derivatives are nucleic acid sequences or amino acid sequences formed from the native compounds either directly or by modification or partial substitution. Analogs are nucleic acid sequences or amino acid sequences that have a structure similar to, but not identical to, the native compound but differs from it in respect to certain components or side
10 chains. Analogs may be synthetic or from a different evolutionary origin and may have a similar or opposite metabolic activity compared to wild type. Homologs are nucleic acid sequences or amino acid sequences of a particular gene that are derived from different species.

Derivatives and analogs may be full length or other than full length, if the derivative or analog contains a modified nucleic acid or amino acid, as described below. Derivatives or
15 analogs of the nucleic acids or proteins of the invention include, but are not limited to, molecules comprising regions that are substantially homologous to the nucleic acids or proteins of the invention, in various embodiments, by at least about 70%, 80%, or 95% identity (with a preferred identity of 80-95%) over a nucleic acid or amino acid sequence of identical size or when compared to an aligned sequence in which the alignment is done by a
20 computer homology program known in the art, or whose encoding nucleic acid is capable of hybridizing to the complement of a sequence encoding the aforementioned proteins under stringent, moderately stringent, or low stringent conditions. *See e.g.* Ausubel, *et al.*, CURRENT PROTOCOLS IN MOLECULAR BIOLOGY, John Wiley & Sons, New York, NY, 1993, and below.

A "homologous nucleic acid sequence" or "homologous amino acid sequence," or
25 variations thereof, refer to sequences characterized by a homology at the nucleotide level or amino acid level as discussed above. Homologous nucleotide sequences encode those sequences coding for isoforms of NOVX polypeptides. Isoforms can be expressed in different tissues of the same organism as a result of, for example, alternative splicing of RNA. Alternatively, isoforms can be encoded by different genes. In the invention, homologous
30 nucleotide sequences include nucleotide sequences encoding for an NOVX polypeptide of species other than humans, including, but not limited to: vertebrates, and thus can include, *e.g.*, frog, mouse, rat, rabbit, dog, cat cow, horse, and other organisms. Homologous nucleotide sequences also include, but are not limited to, naturally occurring allelic variations and mutations of the nucleotide sequences set forth herein. A homologous nucleotide sequence

does not, however, include the exact nucleotide sequence encoding human NOVX protein. Homologous nucleic acid sequences include those nucleic acid sequences that encode conservative amino acid substitutions (see below) in SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, and 217, as well as a polypeptide possessing NOVX biological activity. Various biological activities of the NOVX proteins are described below.

An NOVX polypeptide is encoded by the open reading frame ("ORF") of an NOVX nucleic acid. An ORF corresponds to a nucleotide sequence that could potentially be translated into a polypeptide. A stretch of nucleic acids comprising an ORF is uninterrupted by a stop codon. An ORF that represents the coding sequence for a full protein begins with an ATG "start" codon and terminates with one of the three "stop" codons, namely, TAA, TAG, or TGA. For the purposes of this invention, an ORF may be any part of a coding sequence, with or without a start codon, a stop codon, or both. For an ORF to be considered as a good candidate for coding for a *bona fide* cellular protein, a minimum size requirement is often set, e.g., a stretch of DNA that would encode a protein of 50 amino acids or more.

The nucleotide sequences determined from the cloning of the human NOVX genes allows for the generation of probes and primers designed for use in identifying and/or cloning NOVX homologues in other cell types, e.g. from other tissues, as well as NOVX homologues from other vertebrates. The probe/primer typically comprises substantially purified oligonucleotide. The oligonucleotide typically comprises a region of nucleotide sequence that hybridizes under stringent conditions to at least about 12, 25, 50, 100, 150, 200, 250, 300, 350 or 400 consecutive sense strand nucleotide sequence SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, or 217; or an anti-sense strand nucleotide sequence of SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, or 217; or of a naturally occurring mutant of SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, and 217.

Probes based on the human NOVX nucleotide sequences can be used to detect transcripts or genomic sequences encoding the same or homologous proteins. In various embodiments, the probe further comprises a label group attached thereto, e.g. the label group can be a radioisotope, a fluorescent compound, an enzyme, or an enzyme co-factor. Such probes can be used as a part of a diagnostic test kit for identifying cells or tissues which mis-express an NOVX protein, such as by measuring a level of an NOVX-encoding nucleic acid in a sample of cells from a subject e.g., detecting NOVX mRNA levels or determining whether a genomic NOVX gene has been mutated or deleted.

"A polypeptide having a biologically-active portion of an NOVX polypeptide" refers to polypeptides exhibiting activity similar, but not necessarily identical to, an activity of a

polypeptide of the invention, including mature forms, as measured in a particular biological assay, with or without dose dependency. A nucleic acid fragment encoding a "biologically-active portion of NOVX" can be prepared by isolating a portion SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, or 217, that encodes a polypeptide having an NOVX biological activity (the biological activities of the NOVX proteins are described below),
 5 expressing the encoded portion of NOVX protein (*e.g.*, by recombinant expression *in vitro*) and assessing the activity of the encoded portion of NOVX.

NOVX Nucleic Acid and Polypeptide Variants

The invention further encompasses nucleic acid molecules that differ from the
 10 nucleotide sequences shown in SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, and 217 due to degeneracy of the genetic code and thus encode the same NOVX proteins as that encoded by the nucleotide sequences shown in SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, and 217. In another embodiment, an isolated nucleic acid molecule of the invention has a nucleotide sequence encoding a protein having an amino
 15 acid sequence shown in SEQ ID NOS:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, or 218.

In addition to the human NOVX nucleotide sequences shown in SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, and 217, it will be appreciated by those skilled in the art that DNA sequence polymorphisms that lead to changes in the amino acid sequences
 20 of the NOVX polypeptides may exist within a population (*e.g.*, the human population). Such genetic polymorphism in the NOVX genes may exist among individuals within a population due to natural allelic variation. As used herein, the terms "gene" and "recombinant gene" refer to nucleic acid molecules comprising an open reading frame (ORF) encoding an NOVX protein, preferably a vertebrate NOVX protein. Such natural allelic variations can typically
 25 result in 1-5% variance in the nucleotide sequence of the NOVX genes. Any and all such nucleotide variations and resulting amino acid polymorphisms in the NOVX polypeptides, which are the result of natural allelic variation and that do not alter the functional activity of the NOVX polypeptides, are intended to be within the scope of the invention.

Moreover, nucleic acid molecules encoding NOVX proteins from other species, and
 30 thus that have a nucleotide sequence that differs from the human SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, and 217 are intended to be within the scope of the invention. Nucleic acid molecules corresponding to natural allelic variants and homologues of the NOVX cDNAs of the invention can be isolated based on their homology to the human

NOVX nucleic acids disclosed herein using the human cDNAs, or a portion thereof, as a hybridization probe according to standard hybridization techniques under stringent hybridization conditions.

Accordingly, in another embodiment, an isolated nucleic acid molecule of the invention is at least 6 nucleotides in length and hybridizes under stringent conditions to the nucleic acid molecule comprising the nucleotide sequence of SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, and 217. In another embodiment, the nucleic acid is at least 10, 25, 50, 100, 250, 500, 750, 1000, 1500, or 2000 or more nucleotides in length. In yet another embodiment, an isolated nucleic acid molecule of the invention hybridizes to the coding region. As used herein, the term "hybridizes under stringent conditions" is intended to describe conditions for hybridization and washing under which nucleotide sequences at least 60% homologous to each other typically remain hybridized to each other.

Homologs (*i.e.*, nucleic acids encoding NOVX proteins derived from species other than human) or other related sequences (*e.g.*, paralogs) can be obtained by low, moderate or high stringency hybridization with all or a portion of the particular human sequence as a probe using methods well known in the art for nucleic acid hybridization and cloning.

As used herein, the phrase "stringent hybridization conditions" refers to conditions under which a probe, primer or oligonucleotide will hybridize to its target sequence, but to no other sequences. Stringent conditions are sequence-dependent and will be different in different circumstances. Longer sequences hybridize specifically at higher temperatures than shorter sequences. Generally, stringent conditions are selected to be about 5 °C lower than the thermal melting point (T_m) for the specific sequence at a defined ionic strength and pH. The T_m is the temperature (under defined ionic strength, pH and nucleic acid concentration) at which 50% of the probes complementary to the target sequence hybridize to the target sequence at equilibrium. Since the target sequences are generally present at excess, at T_m, 50% of the probes are occupied at equilibrium. Typically, stringent conditions will be those in which the salt concentration is less than about 1.0 M sodium ion, typically about 0.01 to 1.0 M sodium ion (or other salts) at pH 7.0 to 8.3 and the temperature is at least about 30°C for short probes, primers or oligonucleotides (*e.g.*, 10 nt to 50 nt) and at least about 60°C for longer probes, primers and oligonucleotides. Stringent conditions may also be achieved with the addition of destabilizing agents, such as formamide.

Stringent conditions are known to those skilled in the art and can be found in Ausubel, *et al.*, (eds.), CURRENT PROTOCOLS IN MOLECULAR BIOLOGY, John Wiley & Sons, N.Y.

(1989), 6.3.1-6.3.6. Preferably, the conditions are such that sequences at least about 65%, 70%, 75%, 85%, 90%, 95%, 98%, or 99% homologous to each other typically remain hybridized to each other. A non-limiting example of stringent hybridization conditions are hybridization in a high salt buffer comprising 6X SSC, 50 mM Tris-HCl (pH 7.5), 1 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.02% BSA, and 500 mg/ml denatured salmon sperm DNA at 65°C, followed by one or more washes in 0.2X SSC, 0.01% BSA at 50°C. An isolated nucleic acid molecule of the invention that hybridizes under stringent conditions to the sequences SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, and 217, corresponds to a naturally-occurring nucleic acid molecule. As used herein, a "naturally-occurring" nucleic acid molecule refers to an RNA or DNA molecule having a nucleotide sequence that occurs in nature (*e.g.*, encodes a natural protein).

In a second embodiment, a nucleic acid sequence that is hybridizable to the nucleic acid molecule comprising the nucleotide sequence of SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, and 217, or fragments, analogs or derivatives thereof, under conditions of moderate stringency is provided. A non-limiting example of moderate stringency hybridization conditions are hybridization in 6X SSC, 5X Denhardt's solution, 0.5% SDS and 100 mg/ml denatured salmon sperm DNA at 55°C, followed by one or more washes in 1X SSC, 0.1% SDS at 37°C. Other conditions of moderate stringency that may be used are well-known within the art. *See, e.g.*, Ausubel, *et al.* (eds.), 1993, CURRENT PROTOCOLS IN MOLECULAR BIOLOGY, John Wiley & Sons, NY, and Kriegler, 1990; GENE TRANSFER AND EXPRESSION, A LABORATORY MANUAL, Stockton Press, NY.

In a third embodiment, a nucleic acid that is hybridizable to the nucleic acid molecule comprising the nucleotide sequences SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, and 217, or fragments, analogs or derivatives thereof, under conditions of low stringency, is provided. A non-limiting example of low stringency hybridization conditions are hybridization in 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 mg/ml denatured salmon sperm DNA, 10% (wt/vol) dextran sulfate at 40°C, followed by one or more washes in 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS at 50°C. Other conditions of low stringency that may be used are well known in the art (*e.g.*, as employed for cross-species hybridizations). *See, e.g.*, Ausubel, *et al.* (eds.), 1993, CURRENT PROTOCOLS IN MOLECULAR BIOLOGY, John Wiley & Sons, NY, and Kriegler, 1990, GENE TRANSFER AND EXPRESSION, A LABORATORY MANUAL, Stockton Press, NY; Shilo and Weinberg, 1981. *Proc Natl Acad Sci USA* 78: 6789-6792.

Conservative Mutations

In addition to naturally-occurring allelic variants of NOVX sequences that may exist in the population, the skilled artisan will further appreciate that changes can be introduced by mutation into the nucleotide sequences SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, and 217, thereby leading to changes in the amino acid sequences of the encoded NOVX proteins, without altering the functional ability of said NOVX proteins. For example, nucleotide substitutions leading to amino acid substitutions at "non-essential" amino acid residues can be made in the sequence SEQ ID NOS:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, or 218. A "non-essential" amino acid residue is a residue that can be altered from the wild-type sequences of the NOVX proteins without altering their biological activity, whereas an "essential" amino acid residue is required for such biological activity. For example, amino acid residues that are conserved among the NOVX proteins of the invention are predicted to be particularly non-amenable to alteration. Amino acids for which conservative substitutions can be made are well-known within the art.

Another aspect of the invention pertains to nucleic acid molecules encoding NOVX proteins that contain changes in amino acid residues that are not essential for activity. Such NOVX proteins differ in amino acid sequence from SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, and 217 yet retain biological activity. In one embodiment, the isolated nucleic acid molecule comprises a nucleotide sequence encoding a protein, wherein the protein comprises an amino acid sequence at least about 45% homologous to the amino acid sequences SEQ ID NOS:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, and 218. Preferably, the protein encoded by the nucleic acid molecule is at least about 60% homologous to SEQ ID NOS:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, and 218; more preferably at least about 70% homologous SEQ ID NOS:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, or 218; still more preferably at least about 80% homologous to SEQ ID NOS:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, or 218; even more preferably at least about 90% homologous to SEQ ID NOS:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, or 218; and most preferably at least about 95% homologous to SEQ ID NOS:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, or 218.

An isolated nucleic acid molecule encoding an NOVX protein homologous to the protein of SEQ ID NOS:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, or 218 can be created by introducing one or more nucleotide substitutions, additions or deletions into the nucleotide sequence of SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31,

and 217, such that one or more amino acid substitutions, additions or deletions are introduced into the encoded protein.

Mutations can be introduced into SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, and 217 by standard techniques, such as site-directed mutagenesis and PCR-mediated mutagenesis. Preferably, conservative amino acid substitutions are made at one or more predicted, non-essential amino acid residues. A "conservative amino acid substitution" is one in which the amino acid residue is replaced with an amino acid residue having a similar side chain. Families of amino acid residues having similar side chains have been defined within the art. These families include amino acids with basic side chains (*e.g.*, lysine, arginine, histidine), acidic side chains (*e.g.*, aspartic acid, glutamic acid), uncharged polar side chains (*e.g.*, glycine, asparagine, glutamine, serine, threonine, tyrosine, cysteine), nonpolar side chains (*e.g.*, alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine, tryptophan), beta-branched side chains (*e.g.*, threonine, valine, isoleucine) and aromatic side chains (*e.g.*, tyrosine, phenylalanine, tryptophan, histidine). Thus, a predicted non-essential amino acid residue in the NOVX protein is replaced with another amino acid residue from the same side chain family. Alternatively, in another embodiment, mutations can be introduced randomly along all or part of an NOVX coding sequence, such as by saturation mutagenesis, and the resultant mutants can be screened for NOVX biological activity to identify mutants that retain activity. Following mutagenesis SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, and 217, the encoded protein can be expressed by any recombinant technology known in the art and the activity of the protein can be determined.

The relatedness of amino acid families may also be determined based on side chain interactions. Substituted amino acids may be fully conserved "strong" residues or fully conserved "weak" residues. The "strong" group of conserved amino acid residues may be any one of the following groups: STA, NEQK, NHQK, NDEQ, QHRK, MILV, MILF, HY, FYW, wherein the single letter amino acid codes are grouped by those amino acids that may be substituted for each other. Likewise, the "weak" group of conserved residues may be any one of the following: CSA, ATV, SAG, STNK, STPA, SGND, SNDEQK, NDEQHK, NEQHRK, VLIM, HFY, wherein the letters within each group represent the single letter amino acid code.

In one embodiment, a mutant NOVX protein can be assayed for (i) the ability to form protein:protein interactions with other NOVX proteins, other cell-surface proteins, or biologically-active portions thereof, (ii) complex formation between a mutant NOVX protein and an NOVX ligand; or (iii) the ability of a mutant NOVX protein to bind to an intracellular target protein or biologically-active portion thereof; (*e.g.* avidin proteins).

In yet another embodiment, a mutant NOVX protein can be assayed for the ability to regulate a specific biological function (*e.g.*, regulation of insulin release).

Antisense Nucleic Acids

Another aspect of the invention pertains to isolated antisense nucleic acid molecules
 5 that are hybridizable to or complementary to the nucleic acid molecule comprising the
 nucleotide sequence of SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31,
 and 217, or fragments, analogs or derivatives thereof. An "antisense" nucleic acid comprises a
 nucleotide sequence that is complementary to a "sense" nucleic acid encoding a protein (*e.g.*,
 complementary to the coding strand of a double-stranded cDNA molecule or complementary
 10 to an mRNA sequence). In specific aspects, antisense nucleic acid molecules are provided that
 comprise a sequence complementary to at least about 10, 25, 50, 100, 250 or 500 nucleotides
 or an entire NOVX coding strand, or to only a portion thereof. Nucleic acid molecules
 encoding fragments, homologs, derivatives and analogs of an NOVX protein of SEQ ID
 NOS:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, or 218, or antisense nucleic acids
 15 complementary to an NOVX nucleic acid sequence of SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15,
 17, 19, 21, 23, 25, 27, 29, 31, and 217, are additionally provided.

In one embodiment, an antisense nucleic acid molecule is antisense to a "coding
 region" of the coding strand of a nucleotide sequence encoding an NOVX protein. The term
 "coding region" refers to the region of the nucleotide sequence comprising codons which are
 20 translated into amino acid residues. In another embodiment, the antisense nucleic acid
 molecule is antisense to a "noncoding region" of the coding strand of a nucleotide sequence
 encoding the NOVX protein. The term "noncoding region" refers to 5' and 3' sequences which
 flank the coding region that are not translated into amino acids (*i.e.*, also referred to as 5' and
 3' untranslated regions).

25 Given the coding strand sequences encoding the NOVX protein disclosed herein,
 antisense nucleic acids of the invention can be designed according to the rules of Watson and
 Crick or Hoogsteen base pairing. The antisense nucleic acid molecule can be complementary
 to the entire coding region of NOVX mRNA, but more preferably is an oligonucleotide that is
 antisense to only a portion of the coding or noncoding region of NOVX mRNA. For example,
 30 the antisense oligonucleotide can be complementary to the region surrounding the translation
 start site of NOVX mRNA. An antisense oligonucleotide can be, for example, about 5, 10, 15,
 20, 25, 30, 35, 40, 45 or 50 nucleotides in length. An antisense nucleic acid of the invention
 can be constructed using chemical synthesis or enzymatic ligation reactions using procedures

known in the art. For example, an antisense nucleic acid (*e.g.*, an antisense oligonucleotide) can be chemically synthesized using naturally-occurring nucleotides or variously modified nucleotides designed to increase the biological stability of the molecules or to increase the physical stability of the duplex formed between the antisense and sense nucleic acids (*e.g.*, phosphorothioate derivatives and acridine substituted nucleotides can be used).

Examples of modified nucleotides that can be used to generate the antisense nucleic acid include: 5-fluorouracil, 5-bromouracil, 5-chlorouracil, 5-iodouracil, hypoxanthine, xanthine, 4-acetylcytosine, 5-(carboxyhydroxymethyl) uracil, 5-carboxymethylaminomethyl-2-thiouridine, 5-carboxymethylaminomethyluracil, dihydrouracil, beta-D-galactosylqueosine, inosine, N6-isopentenyladenine, 1-methylguanine, 1-methylinosine, 2,2-dimethylguanine, 2-methyladenine, 2-methylguanine, 3-methylcytosine, 5-methylcytosine, N6-adenine, 7-methylguanine, 5-methylaminomethyluracil, 5-methoxyaminomethyl-2-thiouracil, beta-D-mannosylqueosine, 5'-methoxycarboxymethyluracil, 5-methoxyuracil, 2-methylthio-N6-isopentenyladenine, uracil-5-oxyacetic acid (v), wybutoxosine, pseudouracil, queosine, 2-thiocytosine, 5-methyl-2-thiouracil, 2-thiouracil, 4-thiouracil, 5-methyluracil, uracil-5-oxyacetic acid methylester, uracil-5-oxyacetic acid (v), 5-methyl-2-thiouracil, 3-(3-amino-3-N-2-carboxypropyl) uracil, (acp3)w, and 2,6-diaminopurine. Alternatively, the antisense nucleic acid can be produced biologically using an expression vector into which a nucleic acid has been subcloned in an antisense orientation (*i.e.*, RNA transcribed from the inserted nucleic acid will be of an antisense orientation to a target nucleic acid of interest, described further in the following subsection).

The antisense nucleic acid molecules of the invention are typically administered to a subject or generated *in situ* such that they hybridize with or bind to cellular mRNA and/or genomic DNA encoding an NOVX protein to thereby inhibit expression of the protein (*e.g.*, by inhibiting transcription and/or translation). The hybridization can be by conventional nucleotide complementarity to form a stable duplex, or, for example, in the case of an antisense nucleic acid molecule that binds to DNA duplexes, through specific interactions in the major groove of the double helix. An example of a route of administration of antisense nucleic acid molecules of the invention includes direct injection at a tissue site. Alternatively, antisense nucleic acid molecules can be modified to target selected cells and then administered systemically. For example, for systemic administration, antisense molecules can be modified such that they specifically bind to receptors or antigens expressed on a selected cell surface (*e.g.*, by linking the antisense nucleic acid molecules to peptides or antibodies that bind to cell surface receptors or antigens). The antisense nucleic acid molecules can also be delivered to

cells using the vectors described herein. To achieve sufficient nucleic acid molecules, vector constructs in which the antisense nucleic acid molecule is placed under the control of a strong pol II or pol III promoter are preferred.

In yet another embodiment, the antisense nucleic acid molecule of the invention is an
 5 α -anomeric nucleic acid molecule. An α -anomeric nucleic acid molecule forms specific double-stranded hybrids with complementary RNA in which, contrary to the usual β -units, the strands run parallel to each other. *See, e.g., Gaultier, et al., 1987. Nucl. Acids Res. 15: 6625-6641.* The antisense nucleic acid molecule can also comprise a
 2'-o-methylribonucleotide (*See, e.g., Inoue, et al. 1987. Nucl. Acids Res. 15: 6131-6148*) or a
 10 chimeric RNA-DNA analogue (*See, e.g., Inoue, et al., 1987. FEBS Lett. 215: 327-330.*)

Ribozymes and PNA Moieties

Nucleic acid modifications include, by way of non-limiting example, modified bases, and nucleic acids whose sugar phosphate backbones are modified or derivatized. These
 15 modifications are carried out at least in part to enhance the chemical stability of the modified nucleic acid, such that they may be used, for example, as antisense binding nucleic acids in therapeutic applications in a subject.

In one embodiment, an antisense nucleic acid of the invention is a ribozyme. Ribozymes are catalytic RNA molecules with ribonuclease activity that are capable of
 20 cleaving a single-stranded nucleic acid, such as an mRNA, to which they have a complementary region. Thus, ribozymes (*e.g., hammerhead ribozymes as described in Haselhoff and Gerlach 1988. Nature 334: 585-591*) can be used to catalytically cleave NOVX mRNA transcripts to thereby inhibit translation of NOVX mRNA. A ribozyme having specificity for an NOVX-encoding nucleic acid can be designed based upon the nucleotide
 25 sequence of an NOVX cDNA disclosed herein (*i.e., SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, and 217*). For example, a derivative of a *Tetrahymena* L-19 IVS RNA can be constructed in which the nucleotide sequence of the active site is complementary to the nucleotide sequence to be cleaved in an NOVX-encoding mRNA. *See, e.g., U.S. Patent 4,987,071 to Cech, et al. and U.S. Patent 5,116,742 to Cech, et al.* NOVX mRNA can also be
 30 used to select a catalytic RNA having a specific ribonuclease activity from a pool of RNA molecules. *See, e.g., Bartel et al., (1993) Science 261:1411-1418.*

Alternatively, NOVX gene expression can be inhibited by targeting nucleotide sequences complementary to the regulatory region of the NOVX nucleic acid (*e.g., the NOVX promoter and/or enhancers*) to form triple helical structures that prevent transcription of the

NOVX gene in target cells. *See, e.g.,* Helene, 1991. *Anticancer Drug Des.* 6: 569-84; Helene, *et al.* 1992. *Ann. N.Y. Acad. Sci.* 660: 27-36; Maher, 1992. *Bioassays* 14: 807-15.

In various embodiments, the NOVX nucleic acids can be modified at the base moiety, sugar moiety or phosphate backbone to improve, *e.g.,* the stability, hybridization, or solubility of the molecule. For example, the deoxyribose phosphate backbone of the nucleic acids can be modified to generate peptide nucleic acids. *See, e.g.,* Hyrup, *et al.*, 1996. *Bioorg Med Chem* 4: 5-23. As used herein, the terms "peptide nucleic acids" or "PNAs" refer to nucleic acid mimics (*e.g.,* DNA mimics) in which the deoxyribose phosphate backbone is replaced by a pseudopeptide backbone and only the four natural nucleobases are retained. The neutral backbone of PNAs has been shown to allow for specific hybridization to DNA and RNA under conditions of low ionic strength. The synthesis of PNA oligomers can be performed using standard solid phase peptide synthesis protocols as described in Hyrup, *et al.*, 1996. *supra*; Perry-O'Keefe, *et al.*, 1996. *Proc. Natl. Acad. Sci. USA* 93: 14670-14675.

PNAs of NOVX can be used in therapeutic and diagnostic applications. For example, PNAs can be used as antisense or antigene agents for sequence-specific modulation of gene expression by, *e.g.,* inducing transcription or translation arrest or inhibiting replication. PNAs of NOVX can also be used, for example, in the analysis of single base pair mutations in a gene (*e.g.,* PNA directed PCR clamping; as artificial restriction enzymes when used in combination with other enzymes, *e.g.,* S_I nucleases (*See, Hyrup, et al.*, 1996.*supra*); or as probes or primers for DNA sequence and hybridization (*See, Hyrup, et al.*, 1996, *supra*; Perry-O'Keefe, *et al.*, 1996. *supra*).

In another embodiment, PNAs of NOVX can be modified, *e.g.,* to enhance their stability or cellular uptake, by attaching lipophilic or other helper groups to PNA, by the formation of PNA-DNA chimeras, or by the use of liposomes or other techniques of drug delivery known in the art. For example, PNA-DNA chimeras of NOVX can be generated that may combine the advantageous properties of PNA and DNA. Such chimeras allow DNA recognition enzymes (*e.g.,* RNase H and DNA polymerases) to interact with the DNA portion while the PNA portion would provide high binding affinity and specificity. PNA-DNA chimeras can be linked using linkers of appropriate lengths selected in terms of base stacking, number of bonds between the nucleobases, and orientation (*see, Hyrup, et al.*, 1996. *supra*). The synthesis of PNA-DNA chimeras can be performed as described in Hyrup, *et al.*, 1996. *supra* and Finn, *et al.*, 1996. *Nucl Acids Res* 24: 3357-3363. For example, a DNA chain can be synthesized on a solid support using standard phosphoramidite coupling chemistry, and modified nucleoside analogs, *e.g.,* 5'-(4-methoxytrityl)amino-5'-deoxy-thymidine

phosphoramidite, can be used between the PNA and the 5' end of DNA. *See, e.g.,* Mag, *et al.*, 1989. *Nucl Acid Res* 17: 5973-5988. PNA monomers are then coupled in a stepwise manner to produce a chimeric molecule with a 5' PNA segment and a 3' DNA segment. *See, e.g.,* Finn, *et al.*, 1996. *supra*. Alternatively, chimeric molecules can be synthesized with a 5' DNA segment and a 3' PNA segment. *See, e.g.,* Petersen, *et al.*, 1975. *Bioorg. Med. Chem. Lett.* 5: 1119-11124.

In other embodiments, the oligonucleotide may include other appended groups such as peptides (*e.g.*, for targeting host cell receptors *in vivo*), or agents facilitating transport across the cell membrane (*see, e.g.,* Letsinger, *et al.*, 1989. *Proc. Natl. Acad. Sci. U.S.A.* 86: 6553-6556; Lemaitre, *et al.*, 1987. *Proc. Natl. Acad. Sci.* 84: 648-652; PCT Publication No. WO88/09810) or the blood-brain barrier (*see, e.g.,* PCT Publication No. WO 89/10134). In addition, oligonucleotides can be modified with hybridization triggered cleavage agents (*see, e.g.,* Krol, *et al.*, 1988. *BioTechniques* 6:958-976) or intercalating agents (*see, e.g.,* Zon, 1988. *Pharm. Res.* 5: 539-549). To this end, the oligonucleotide may be conjugated to another molecule, *e.g.*, a peptide, a hybridization triggered cross-linking agent, a transport agent, a hybridization-triggered cleavage agent, and the like.

NOVX Polypeptides

A polypeptide according to the invention includes a polypeptide including the amino acid sequence of NOVX polypeptides whose sequences are provided in SEQ ID NOS:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, or 218. The invention also includes a mutant or variant protein any of whose residues may be changed from the corresponding residues shown in SEQ ID NOS:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, or 218 while still encoding a protein that maintains its NOVX activities and physiological functions, or a functional fragment thereof.

In general, an NOVX variant that preserves NOVX-like function includes any variant in which residues at a particular position in the sequence have been substituted by other amino acids, and further include the possibility of inserting an additional residue or residues between two residues of the parent protein as well as the possibility of deleting one or more residues from the parent sequence. Any amino acid substitution, insertion, or deletion is encompassed by the invention. In favorable circumstances, the substitution is a conservative substitution as defined above.

One aspect of the invention pertains to isolated NOVX proteins, and biologically-active portions thereof, or derivatives, fragments, analogs or homologs thereof. Also provided

are polypeptide fragments suitable for use as immunogens to raise anti-NOVX antibodies. In one embodiment, native NOVX proteins can be isolated from cells or tissue sources by an appropriate purification scheme using standard protein purification techniques. In another embodiment, NOVX proteins are produced by recombinant DNA techniques. Alternative to
5 recombinant expression, an NOVX protein or polypeptide can be synthesized chemically using standard peptide synthesis techniques.

An "isolated" or "purified" polypeptide or protein or biologically-active portion thereof is substantially free of cellular material or other contaminating proteins from the cell or tissue source from which the NOVX protein is derived, or substantially free from chemical
10 precursors or other chemicals when chemically synthesized. The language "substantially free of cellular material" includes preparations of NOVX proteins in which the protein is separated from cellular components of the cells from which it is isolated or recombinantly-produced. In one embodiment, the language "substantially free of cellular material" includes preparations of NOVX proteins having less than about 30% (by dry weight) of non-NOVX proteins (also
15 referred to herein as a "contaminating protein"), more preferably less than about 20% of non-NOVX proteins, still more preferably less than about 10% of non-NOVX proteins, and most preferably less than about 5% of non-NOVX proteins. When the NOVX protein or biologically-active portion thereof is recombinantly-produced, it is also preferably substantially free of culture medium, *i.e.*, culture medium represents less than about 20%,
20 more preferably less than about 10%, and most preferably less than about 5% of the volume of the NOVX protein preparation.

The language "substantially free of chemical precursors or other chemicals" includes preparations of NOVX proteins in which the protein is separated from chemical precursors or other chemicals that are involved in the synthesis of the protein. In one embodiment, the
25 language "substantially free of chemical precursors or other chemicals" includes preparations of NOVX proteins having less than about 30% (by dry weight) of chemical precursors or non-NOVX chemicals, more preferably less than about 20% chemical precursors or non-NOVX chemicals, still more preferably less than about 10% chemical precursors or non-NOVX chemicals, and most preferably less than about 5% chemical precursors or
30 non-NOVX chemicals.

Biologically-active portions of NOVX proteins include peptides comprising amino acid sequences sufficiently homologous to or derived from the amino acid sequences of the NOVX proteins (*e.g.*, the amino acid sequence shown in SEQ ID NOS:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, or 218) that include fewer amino acids than the full-length

NOVX proteins, and exhibit at least one activity of an NOVX protein. Typically, biologically-active portions comprise a domain or motif with at least one activity of the NOVX protein. A biologically-active portion of an NOVX protein can be a polypeptide which is, for example, 10, 25, 50, 100 or more amino acid residues in length.

5 Moreover, other biologically-active portions, in which other regions of the protein are deleted, can be prepared by recombinant techniques and evaluated for one or more of the functional activities of a native NOVX protein.

In an embodiment, the NOVX protein has an amino acid sequence shown SEQ ID NOS:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, or 218. In other embodiments, 10 the NOVX protein is substantially homologous to SEQ ID NOS:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, or 218, and retains the functional activity of the protein of SEQ ID NOS:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, or 218, yet differs in amino acid sequence due to natural allelic variation or mutagenesis, as described in detail, below.

Accordingly, in another embodiment, the NOVX protein is a protein that comprises an amino 15 acid sequence at least about 45% homologous to the amino acid sequence SEQ ID NOS:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, or 218, and retains the functional activity of the NOVX proteins of SEQ ID NOS:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, or 218.

20 **Determining Homology Between Two or More Sequences**

To determine the percent homology of two amino acid sequences or of two nucleic acids, the sequences are aligned for optimal comparison purposes (*e.g.*, gaps can be introduced in the sequence of a first amino acid or nucleic acid sequence for optimal alignment with a second amino or nucleic acid sequence). The amino acid residues or nucleotides at 25 corresponding amino acid positions or nucleotide positions are then compared. When a position in the first sequence is occupied by the same amino acid residue or nucleotide as the corresponding position in the second sequence, then the molecules are homologous at that position (*i.e.*, as used herein amino acid or nucleic acid "homology" is equivalent to amino acid or nucleic acid "identity").

30 The nucleic acid sequence homology may be determined as the degree of identity between two sequences. The homology may be determined using computer programs known in the art, such as GAP software provided in the GCG program package. *See*, Needleman and Wunsch, 1970. *J Mol Biol* 48: 443-453. Using GCG GAP software with the following settings for nucleic acid sequence comparison: GAP creation penalty of 5.0 and GAP extension

penalty of 0.3, the coding region of the analogous nucleic acid sequences referred to above exhibits a degree of identity preferably of at least 70%, 75%, 80%, 85%, 90%, 95%, 98%, or 99%, with the CDS (encoding) part of the DNA sequence shown in SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, and 217.

5 The term "sequence identity" refers to the degree to which two polynucleotide or polypeptide sequences are identical on a residue-by-residue basis over a particular region of comparison. The term "percentage of sequence identity" is calculated by comparing two optimally aligned sequences over that region of comparison, determining the number of positions at which the identical nucleic acid base (*e.g.*, A, T, C, G, U, or I, in the case of
10 nucleic acids) occurs in both sequences to yield the number of matched positions, dividing the number of matched positions by the total number of positions in the region of comparison (*i.e.*, the window size), and multiplying the result by 100 to yield the percentage of sequence identity. The term "substantial identity" as used herein denotes a characteristic of a polynucleotide sequence, wherein the polynucleotide comprises a sequence that has at least 80
15 percent sequence identity, preferably at least 85 percent identity and often 90 to 95 percent sequence identity, more usually at least 99 percent sequence identity as compared to a reference sequence over a comparison region.

Chimeric and Fusion Proteins

20 The invention also provides NOVX chimeric or fusion proteins. As used herein, an NOVX "chimeric protein" or "fusion protein" comprises an NOVX polypeptide operatively-linked to a non-NOVX polypeptide. An "NOVX polypeptide" refers to a polypeptide having an amino acid sequence corresponding to an NOVX protein SEQ ID NOS:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, or 218, whereas a "non-NOVX polypeptide" refers to a
25 polypeptide having an amino acid sequence corresponding to a protein that is not substantially homologous to the NOVX protein, *e.g.*, a protein that is different from the NOVX protein and that is derived from the same or a different organism. Within an NOVX fusion protein the NOVX polypeptide can correspond to all or a portion of an NOVX protein. In one embodiment, an NOVX fusion protein comprises at least one biologically-active portion of an
30 NOVX protein. In another embodiment, an NOVX fusion protein comprises at least two biologically-active portions of an NOVX protein. In yet another embodiment, an NOVX fusion protein comprises at least three biologically-active portions of an NOVX protein. Within the fusion protein, the term "operatively-linked" is intended to indicate that the NOVX polypeptide and the non-NOVX polypeptide are fused in-frame with one another. The

non-NOVX polypeptide can be fused to the N-terminus or C-terminus of the NOVX polypeptide.

In one embodiment, the fusion protein is a GST-NOVX fusion protein in which the NOVX sequences are fused to the C-terminus of the GST (glutathione S-transferase) sequences. Such fusion proteins can facilitate the purification of recombinant NOVX polypeptides.

In another embodiment, the fusion protein is an NOVX protein containing a heterologous signal sequence at its N-terminus. In certain host cells (*e.g.*, mammalian host cells), expression and/or secretion of NOVX can be increased through use of a heterologous signal sequence.

In yet another embodiment, the fusion protein is an NOVX-immunoglobulin fusion protein in which the NOVX sequences are fused to sequences derived from a member of the immunoglobulin protein family. The NOVX-immunoglobulin fusion proteins of the invention can be incorporated into pharmaceutical compositions and administered to a subject to inhibit an interaction between an NOVX ligand and an NOVX protein on the surface of a cell, to thereby suppress NOVX-mediated signal transduction *in vivo*. The NOVX-immunoglobulin fusion proteins can be used to affect the bioavailability of an NOVX cognate ligand. Inhibition of the NOVX ligand/NOVX interaction may be useful therapeutically for both the treatment of proliferative and differentiative disorders, as well as modulating (*e.g.* promoting or inhibiting) cell survival. Moreover, the NOVX-immunoglobulin fusion proteins of the invention can be used as immunogens to produce anti-NOVX antibodies in a subject, to purify NOVX ligands, and in screening assays to identify molecules that inhibit the interaction of NOVX with an NOVX ligand.

An NOVX chimeric or fusion protein of the invention can be produced by standard recombinant DNA techniques. For example, DNA fragments coding for the different polypeptide sequences are ligated together in-frame in accordance with conventional techniques, *e.g.*, by employing blunt-ended or stagger-ended termini for ligation, restriction enzyme digestion to provide for appropriate termini, filling-in of cohesive ends as appropriate, alkaline phosphatase treatment to avoid undesirable joining, and enzymatic ligation. In another embodiment, the fusion gene can be synthesized by conventional techniques including automated DNA synthesizers. Alternatively, PCR amplification of gene fragments can be carried out using anchor primers that give rise to complementary overhangs between two consecutive gene fragments that can subsequently be annealed and reamplified to generate a chimeric gene sequence (*see, e.g.*, Ausubel, *et al.* (eds.) CURRENT PROTOCOLS IN MOLECULAR

BIOLOGY, John Wiley & Sons, 1992). Moreover, many expression vectors are commercially available that already encode a fusion moiety (*e.g.*, a GST polypeptide). An NOVX-encoding nucleic acid can be cloned into such an expression vector such that the fusion moiety is linked in-frame to the NOVX protein.

5

NOVX Agonists and Antagonists

The invention also pertains to variants of the NOVX proteins that function as either NOVX agonists (*i.e.*, mimetics) or as NOVX antagonists. Variants of the NOVX protein can be generated by mutagenesis (*e.g.*, discrete point mutation or truncation of the NOVX protein).

10 An agonist of the NOVX protein can retain substantially the same, or a subset of, the biological activities of the naturally occurring form of the NOVX protein. An antagonist of the NOVX protein can inhibit one or more of the activities of the naturally occurring form of the NOVX protein by, for example, competitively binding to a downstream or upstream member of a cellular signaling cascade which includes the NOVX protein. Thus, specific
15 biological effects can be elicited by treatment with a variant of limited function. In one embodiment, treatment of a subject with a variant having a subset of the biological activities of the naturally occurring form of the protein has fewer side effects in a subject relative to treatment with the naturally occurring form of the NOVX proteins.

Variants of the NOVX proteins that function as either NOVX agonists (*i.e.*, mimetics)
20 or as NOVX antagonists can be identified by screening combinatorial libraries of mutants (*e.g.*, truncation mutants) of the NOVX proteins for NOVX protein agonist or antagonist activity. In one embodiment, a variegated library of NOVX variants is generated by combinatorial mutagenesis at the nucleic acid level and is encoded by a variegated gene library. A variegated library of NOVX variants can be produced by, for example,
25 enzymatically ligating a mixture of synthetic oligonucleotides into gene sequences such that a degenerate set of potential NOVX sequences is expressible as individual polypeptides, or alternatively, as a set of larger fusion proteins (*e.g.*, for phage display) containing the set of NOVX sequences therein. There are a variety of methods which can be used to produce libraries of potential NOVX variants from a degenerate oligonucleotide sequence. Chemical
30 synthesis of a degenerate gene sequence can be performed in an automatic DNA synthesizer, and the synthetic gene then ligated into an appropriate expression vector. Use of a degenerate set of genes allows for the provision, in one mixture, of all of the sequences encoding the desired set of potential NOVX sequences. Methods for synthesizing degenerate oligonucleotides are well-known within the art. *See, e.g.*, Narang, 1983. *Tetrahedron* 39: 3;

Itakura, *et al.*, 1984. *Annu. Rev. Biochem.* 53: 323; Itakura, *et al.*, 1984. *Science* 198: 1056; Ike, *et al.*, 1983. *Nucl. Acids Res.* 11: 477.

Polypeptide Libraries

5 In addition, libraries of fragments of the NOVX protein coding sequences can be used to generate a variegated population of NOVX fragments for screening and subsequent selection of variants of an NOVX protein. In one embodiment, a library of coding sequence fragments can be generated by treating a double stranded PCR fragment of an NOVX coding sequence with a nuclease under conditions wherein nicking occurs only about once per
10 molecule, denaturing the double stranded DNA, renaturing the DNA to form double-stranded DNA that can include sense/antisense pairs from different nicked products, removing single stranded portions from reformed duplexes by treatment with S₁ nuclease, and ligating the resulting fragment library into an expression vector. By this method, expression libraries can be derived which encodes N-terminal and internal fragments of various sizes of the NOVX
15 proteins.

Various techniques are known in the art for screening gene products of combinatorial libraries made by point mutations or truncation, and for screening cDNA libraries for gene products having a selected property. Such techniques are adaptable for rapid screening of the gene libraries generated by the combinatorial mutagenesis of NOVX proteins. The most
20 widely used techniques, which are amenable to high throughput analysis, for screening large gene libraries typically include cloning the gene library into replicable expression vectors, transforming appropriate cells with the resulting library of vectors, and expressing the combinatorial genes under conditions in which detection of a desired activity facilitates isolation of the vector encoding the gene whose product was detected. Recursive ensemble
25 mutagenesis (REM), a new technique that enhances the frequency of functional mutants in the libraries, can be used in combination with the screening assays to identify NOVX variants. See, e.g., Arkin and Yourvan, 1992. *Proc. Natl. Acad. Sci. USA* 89: 7811-7815; Delgrave, *et al.*, 1993. *Protein Engineering* 6:327-331.

Anti-NOVX Antibodies

30 Also included in the invention are antibodies to NOVX proteins, or fragments of NOVX proteins. The term "antibody" as used herein refers to immunoglobulin molecules and immunologically active portions of immunoglobulin (Ig) molecules, i.e., molecules that contain an antigen binding site that specifically binds (immunoreacts with) an antigen. Such

antibodies include, but are not limited to, polyclonal, monoclonal, chimeric, single chain, F_{ab} , F_{ab}' and $F_{(ab)2}$ fragments, and an F_{ab} expression library. In general, an antibody molecule obtained from humans relates to any of the classes IgG, IgM, IgA, IgE and IgD, which differ from one another by the nature of the heavy chain present in the molecule. Certain classes have subclasses as well, such as IgG₁, IgG₂, and others. Furthermore, in humans, the light chain may be a kappa chain or a lambda chain. Reference herein to antibodies includes a reference to all such classes, subclasses and types of human antibody species.

An isolated NOVX-related protein of the invention may be intended to serve as an antigen, or a portion or fragment thereof, and additionally can be used as an immunogen to generate antibodies that immunospecifically bind the antigen, using standard techniques for polyclonal and monoclonal antibody preparation. The full-length protein can be used or, alternatively, the invention provides antigenic peptide fragments of the antigen for use as immunogens. An antigenic peptide fragment comprises at least 6 amino acid residues of the amino acid sequence of the full length protein and encompasses an epitope thereof such that an antibody raised against the peptide forms a specific immune complex with the full length protein or with any fragment that contains the epitope. Preferably, the antigenic peptide comprises at least 10 amino acid residues, or at least 15 amino acid residues, or at least 20 amino acid residues, or at least 30 amino acid residues. Preferred epitopes encompassed by the antigenic peptide are regions of the protein that are located on its surface; commonly these are hydrophilic regions.

In certain embodiments of the invention, at least one epitope encompassed by the antigenic peptide is a region of NOVX-related protein that is located on the surface of the protein, *e.g.*, a hydrophilic region. A hydrophobicity analysis of the human NOVX-related protein sequence will indicate which regions of a NOVX-related protein are particularly hydrophilic and, therefore, are likely to encode surface residues useful for targeting antibody production. As a means for targeting antibody production, hydropathy plots showing regions of hydrophilicity and hydrophobicity may be generated by any method well known in the art, including, for example, the Kyte Doolittle or the Hopp Woods methods, either with or without Fourier transformation. See, *e.g.*, Hopp and Woods, 1981, *Proc. Nat. Acad. Sci. USA* 78: 3824-3828; Kyte and Doolittle 1982, *J. Mol. Biol.* 157: 105-142, each of which is incorporated herein by reference in its entirety. Antibodies that are specific for one or more domains within an antigenic protein, or derivatives, fragments, analogs or homologs thereof, are also provided herein.

A protein of the invention, or a derivative, fragment, analog, homolog or ortholog thereof, may be utilized as an immunogen in the generation of antibodies that immunospecifically bind these protein components.

Various procedures known within the art may be used for the production of polyclonal or monoclonal antibodies directed against a protein of the invention, or against derivatives, fragments, analogs homologs or orthologs thereof (see, for example, *Antibodies: A Laboratory Manual*, Harlow and Lane, 1988, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, incorporated herein by reference). Some of these antibodies are discussed below.

10 **Polyclonal Antibodies**

For the production of polyclonal antibodies, various suitable host animals (e.g., rabbit, goat, mouse or other mammal) may be immunized by one or more injections with the native protein, a synthetic variant thereof, or a derivative of the foregoing. An appropriate immunogenic preparation can contain, for example, the naturally occurring immunogenic protein, a chemically synthesized polypeptide representing the immunogenic protein, or a recombinantly expressed immunogenic protein. Furthermore, the protein may be conjugated to a second protein known to be immunogenic in the mammal being immunized. Examples of such immunogenic proteins include but are not limited to keyhole limpet hemocyanin, serum albumin, bovine thyroglobulin, and soybean trypsin inhibitor. The preparation can further include an adjuvant. Various adjuvants used to increase the immunological response include, but are not limited to, Freund's (complete and incomplete), mineral gels (e.g., aluminum hydroxide), surface active substances (e.g., lysolecithin, pluronic polyols, polyanions, peptides, oil emulsions, dinitrophenol, etc.), adjuvants usable in humans such as Bacille Calmette-Guerin and *Corynebacterium parvum*, or similar immunostimulatory agents. Additional examples of adjuvants which can be employed include MPL-TDM adjuvant (monophosphoryl Lipid A, synthetic trehalose dicorynomycolate).

The polyclonal antibody molecules directed against the immunogenic protein can be isolated from the mammal (e.g., from the blood) and further purified by well known techniques, such as affinity chromatography using protein A or protein G, which provide primarily the IgG fraction of immune serum. Subsequently, or alternatively, the specific antigen which is the target of the immunoglobulin sought, or an epitope thereof, may be immobilized on a column to purify the immune specific antibody by immunoaffinity chromatography. Purification of immunoglobulins is discussed, for example, by D. Wilkinson

(The Scientist, published by The Scientist, Inc., Philadelphia PA, Vol. 14, No. 8 (April 17, 2000), pp. 25-28).

Monoclonal Antibodies

5 The term "monoclonal antibody" (MAb) or "monoclonal antibody composition", as used herein, refers to a population of antibody molecules that contain only one molecular species of antibody molecule consisting of a unique light chain gene product and a unique heavy chain gene product. In particular, the complementarity determining regions (CDRs) of the monoclonal antibody are identical in all the molecules of the population. MABs thus
10 contain an antigen binding site capable of immunoreacting with a particular epitope of the antigen characterized by a unique binding affinity for it.

 Monoclonal antibodies can be prepared using hybridoma methods, such as those described by Kohler and Milstein, *Nature*, 256:495 (1975). In a hybridoma method, a mouse, hamster, or other appropriate host animal, is typically immunized with an immunizing agent to
15 elicit lymphocytes that produce or are capable of producing antibodies that will specifically bind to the immunizing agent. Alternatively, the lymphocytes can be immunized in vitro.

 The immunizing agent will typically include the protein antigen, a fragment thereof or a fusion protein thereof. Generally, either peripheral blood lymphocytes are used if cells of human origin are desired, or spleen cells or lymph node cells are used if non-human
20 mammalian sources are desired. The lymphocytes are then fused with an immortalized cell line using a suitable fusing agent, such as polyethylene glycol, to form a hybridoma cell (Goding, MONOCLONAL ANTIBODIES: PRINCIPLES AND PRACTICE, Academic Press, (1986) pp. 59-103). Immortalized cell lines are usually transformed mammalian cells, particularly myeloma cells of rodent, bovine and human origin. Usually, rat or mouse myeloma cell lines
25 are employed. The hybridoma cells can be cultured in a suitable culture medium that preferably contains one or more substances that inhibit the growth or survival of the unfused, immortalized cells. For example, if the parental cells lack the enzyme hypoxanthine guanine phosphoribosyl transferase (HGPRT or HPRT), the culture medium for the hybridomas typically will include hypoxanthine, aminopterin, and thymidine ("HAT medium"), which
30 substances prevent the growth of HGPRT-deficient cells.

 Preferred immortalized cell lines are those that fuse efficiently, support stable high level expression of antibody by the selected antibody-producing cells, and are sensitive to a medium such as HAT medium. More preferred immortalized cell lines are murine myeloma lines, which can be obtained, for instance, from the Salk Institute Cell Distribution Center, San

Diego, California and the American Type Culture Collection, Manassas, Virginia. Human myeloma and mouse-human heteromyeloma cell lines also have been described for the production of human monoclonal antibodies (Kozbor, *J. Immunol.*, 133:3001 (1984); Brodeur et al., MONOCLONAL ANTIBODY PRODUCTION TECHNIQUES AND APPLICATIONS, Marcel Dekker, Inc., New York, (1987) pp. 51-63).

The culture medium in which the hybridoma cells are cultured can then be assayed for the presence of monoclonal antibodies directed against the antigen. Preferably, the binding specificity of monoclonal antibodies produced by the hybridoma cells is determined by immunoprecipitation or by an in vitro binding assay, such as radioimmunoassay (RIA) or enzyme-linked immunoabsorbent assay (ELISA). Such techniques and assays are known in the art. The binding affinity of the monoclonal antibody can, for example, be determined by the Scatchard analysis of Munson and Pollard, *Anal. Biochem.*, 107:220 (1980). Preferably, antibodies having a high degree of specificity and a high binding affinity for the target antigen are isolated.

After the desired hybridoma cells are identified, the clones can be subcloned by limiting dilution procedures and grown by standard methods. Suitable culture media for this purpose include, for example, Dulbecco's Modified Eagle's Medium and RPMI-1640 medium. Alternatively, the hybridoma cells can be grown in vivo as ascites in a mammal.

The monoclonal antibodies secreted by the subclones can be isolated or purified from the culture medium or ascites fluid by conventional immunoglobulin purification procedures such as, for example, protein A-Sepharose, hydroxylapatite chromatography, gel electrophoresis, dialysis, or affinity chromatography.

The monoclonal antibodies can also be made by recombinant DNA methods, such as those described in U.S. Patent No. 4,816,567. DNA encoding the monoclonal antibodies of the invention can be readily isolated and sequenced using conventional procedures (e.g., by using oligonucleotide probes that are capable of binding specifically to genes encoding the heavy and light chains of murine antibodies). The hybridoma cells of the invention serve as a preferred source of such DNA. Once isolated, the DNA can be placed into expression vectors, which are then transfected into host cells such as simian COS cells, Chinese hamster ovary (CHO) cells, or myeloma cells that do not otherwise produce immunoglobulin protein, to obtain the synthesis of monoclonal antibodies in the recombinant host cells. The DNA also can be modified, for example, by substituting the coding sequence for human heavy and light chain constant domains in place of the homologous murine sequences (U.S. Patent No. 4,816,567; Morrison, *Nature* 368, 812-13 (1994)) or by covalently joining to the

immunoglobulin coding sequence all or part of the coding sequence for a non-immunoglobulin polypeptide. Such a non-immunoglobulin polypeptide can be substituted for the constant domains of an antibody of the invention, or can be substituted for the variable domains of one antigen-combining site of an antibody of the invention to create a chimeric bivalent antibody.

5

Humanized Antibodies

The antibodies directed against the protein antigens of the invention can further comprise humanized antibodies or human antibodies. These antibodies are suitable for administration to humans without engendering an immune response by the human against the administered immunoglobulin. Humanized forms of antibodies are chimeric immunoglobulins, immunoglobulin chains or fragments thereof (such as Fv, Fab, Fab', F(ab')₂ or other antigen-binding subsequences of antibodies) that are principally comprised of the sequence of a human immunoglobulin, and contain minimal sequence derived from a non-human immunoglobulin. Humanization can be performed following the method of Winter and co-workers (Jones et al., *Nature*, 321:522-525 (1986); Riechmann et al., *Nature*, 332:323-327 (1988); Verhoeven et al., *Science*, 239:1534-1536 (1988)), by substituting rodent CDRs or CDR sequences for the corresponding sequences of a human antibody. (See also U.S. Patent No. 5,225,539.) In some instances, Fv framework residues of the human immunoglobulin are replaced by corresponding non-human residues. Humanized antibodies can also comprise residues which are found neither in the recipient antibody nor in the imported CDR or framework sequences. In general, the humanized antibody will comprise substantially all of at least one, and typically two, variable domains, in which all or substantially all of the CDR regions correspond to those of a non-human immunoglobulin and all or substantially all of the framework regions are those of a human immunoglobulin consensus sequence. The humanized antibody optimally also will comprise at least a portion of an immunoglobulin constant region (Fc), typically that of a human immunoglobulin (Jones et al., 1986; Riechmann et al., 1988; and Presta, *Curr. Op. Struct. Biol.*, 2:593-596 (1992)).

Human Antibodies

Fully human antibodies relate to antibody molecules in which essentially the entire sequences of both the light chain and the heavy chain, including the CDRs, arise from human genes. Such antibodies are termed "human antibodies", or "fully human antibodies" herein. Human monoclonal antibodies can be prepared by the trioma technique; the human B-cell hybridoma technique (see Kozbor, et al., 1983 *Immunol Today* 4: 72) and the EBV hybridoma

technique to produce human monoclonal antibodies (see Cole, et al., 1985 In: MONOCLONAL ANTIBODIES AND CANCER THERAPY, Alan R. Liss, Inc., pp. 77-96). Human monoclonal antibodies may be utilized in the practice of the present invention and may be produced by using human hybridomas (see Cote, et al., 1983. Proc Natl Acad Sci USA 80: 2026-2030) or
 5 by transforming human B-cells with Epstein Barr Virus in vitro (see Cole, et al., 1985 In: MONOCLONAL ANTIBODIES AND CANCER THERAPY, Alan R. Liss, Inc., pp. 77-96).

In addition, human antibodies can also be produced using additional techniques, including phage display libraries (Hoogenboom and Winter, *J. Mol. Biol.*, 227:381 (1991); Marks et al., *J. Mol. Biol.*, 222:581 (1991)). Similarly, human antibodies can be made by
 10 introducing human immunoglobulin loci into transgenic animals, e.g., mice in which the endogenous immunoglobulin genes have been partially or completely inactivated. Upon challenge, human antibody production is observed, which closely resembles that seen in humans in all respects, including gene rearrangement, assembly, and antibody repertoire. This approach is described, for example, in U.S. Patent Nos. 5,545,807; 5,545,806; 5,569,825;
 15 5,625,126; 5,633,425; 5,661,016, and in Marks et al. (*Bio/Technology* 10, 779-783 (1992)); Lonberg et al. (*Nature* 368 856-859 (1994)); Morrison (*Nature* 368, 812-13 (1994)); Fishwild et al, (*Nature Biotechnology* 14, 845-51 (1996)); Neuberger (*Nature Biotechnology* 14, 826 (1996)); and Lonberg and Huszar (*Intern. Rev. Immunol.* 13 65-93 (1995)).

Human antibodies may additionally be produced using transgenic nonhuman animals
 20 which are modified so as to produce fully human antibodies rather than the animal's endogenous antibodies in response to challenge by an antigen. (See PCT publication WO94/02602). The endogenous genes encoding the heavy and light immunoglobulin chains in the nonhuman host have been incapacitated, and active loci encoding human heavy and light chain immunoglobulins are inserted into the host's genome. The human genes are
 25 incorporated, for example, using yeast artificial chromosomes containing the requisite human DNA segments. An animal which provides all the desired modifications is then obtained as progeny by crossbreeding intermediate transgenic animals containing fewer than the full complement of the modifications. The preferred embodiment of such a nonhuman animal is a mouse, and is termed the XenomouseTM as disclosed in PCT publications WO 96/33735 and
 30 WO 96/34096. This animal produces B cells which secrete fully human immunoglobulins. The antibodies can be obtained directly from the animal after immunization with an immunogen of interest, as, for example, a preparation of a polyclonal antibody, or alternatively from immortalized B cells derived from the animal, such as hybridomas producing monoclonal antibodies. Additionally, the genes encoding the immunoglobulins with human

variable regions can be recovered and expressed to obtain the antibodies directly, or can be further modified to obtain analogs of antibodies such as, for example, single chain Fv molecules.

5 An example of a method of producing a nonhuman host, exemplified as a mouse, lacking expression of an endogenous immunoglobulin heavy chain is disclosed in U.S. Patent No. 5,939,598. It can be obtained by a method including deleting the J segment genes from at least one endogenous heavy chain locus in an embryonic stem cell to prevent rearrangement of the locus and to prevent formation of a transcript of a rearranged immunoglobulin heavy chain locus, the deletion being effected by a targeting vector containing a gene encoding a selectable
10 marker; and producing from the embryonic stem cell a transgenic mouse whose somatic and germ cells contain the gene encoding the selectable marker.

A method for producing an antibody of interest, such as a human antibody, is disclosed in U.S. Patent No. 5,916,771. It includes introducing an expression vector that contains a nucleotide sequence encoding a heavy chain into one mammalian host cell in culture,
15 introducing an expression vector containing a nucleotide sequence encoding a light chain into another mammalian host cell, and fusing the two cells to form a hybrid cell. The hybrid cell expresses an antibody containing the heavy chain and the light chain.

In a further improvement on this procedure, a method for identifying a clinically relevant epitope on an immunogen, and a correlative method for selecting an antibody that
20 binds immunospecifically to the relevant epitope with high affinity, are disclosed in PCT publication WO 99/53049.

F_{ab} Fragments and Single Chain Antibodies

According to the invention, techniques can be adapted for the production of
25 single-chain antibodies specific to an antigenic protein of the invention (see e.g., U.S. Patent No. 4,946,778). In addition, methods can be adapted for the construction of F_{ab} expression libraries (see e.g., Huse, et al., 1989 Science 246: 1275-1281) to allow rapid and effective identification of monoclonal F_{ab} fragments with the desired specificity for a protein or derivatives, fragments, analogs or homologs thereof. Antibody fragments that contain the
30 idiotypes to a protein antigen may be produced by techniques known in the art including, but not limited to: (i) an F_(ab)₂ fragment produced by pepsin digestion of an antibody molecule; (ii) an F_{ab} fragment generated by reducing the disulfide bridges of an F_(ab)₂ fragment; (iii) an F_{ab} fragment generated by the treatment of the antibody molecule with papain and a reducing agent and (iv) F_v fragments.

Bispecific Antibodies

Bispecific antibodies are monoclonal, preferably human or humanized, antibodies that have binding specificities for at least two different antigens. In the present case, one of the binding specificities is for an antigenic protein of the invention. The second binding target is any other antigen, and advantageously is a cell-surface protein or receptor or receptor subunit.

Methods for making bispecific antibodies are known in the art. Traditionally, the recombinant production of bispecific antibodies is based on the co-expression of two immunoglobulin heavy-chain/light-chain pairs, where the two heavy chains have different specificities (Milstein and Cuello, *Nature*, 305:537-539 (1983)). Because of the random assortment of immunoglobulin heavy and light chains, these hybridomas (quadromas) produce a potential mixture of ten different antibody molecules, of which only one has the correct bispecific structure. The purification of the correct molecule is usually accomplished by affinity chromatography steps. Similar procedures are disclosed in WO 93/08829, published 13 May 1993, and in Traunecker *et al.*, 1991 *EMBO J.*, 10:3655-3659.

Antibody variable domains with the desired binding specificities (antibody-antigen combining sites) can be fused to immunoglobulin constant domain sequences. The fusion preferably is with an immunoglobulin heavy-chain constant domain, comprising at least part of the hinge, CH2, and CH3 regions. It is preferred to have the first heavy-chain constant region (CH1) containing the site necessary for light-chain binding present in at least one of the fusions. DNAs encoding the immunoglobulin heavy-chain fusions and, if desired, the immunoglobulin light chain, are inserted into separate expression vectors, and are co-transfected into a suitable host organism. For further details of generating bispecific antibodies see, for example, Suresh *et al.*, *Methods in Enzymology*, 121:210 (1986).

According to another approach described in WO 96/27011, the interface between a pair of antibody molecules can be engineered to maximize the percentage of heterodimers which are recovered from recombinant cell culture. The preferred interface comprises at least a part of the CH3 region of an antibody constant domain. In this method, one or more small amino acid side chains from the interface of the first antibody molecule are replaced with larger side chains (e.g. tyrosine or tryptophan). Compensatory "cavities" of identical or similar size to the large side chain(s) are created on the interface of the second antibody molecule by replacing large amino acid side chains with smaller ones (e.g. alanine or threonine). This provides a mechanism for increasing the yield of the heterodimer over other unwanted end-products such as homodimers.

Bispecific antibodies can be prepared as full length antibodies or antibody fragments (e.g. $F(ab')_2$ bispecific antibodies). Techniques for generating bispecific antibodies from antibody fragments have been described in the literature. For example, bispecific antibodies can be prepared using chemical linkage. Brennan et al., *Science* 229:81 (1985) describe a
 5 procedure wherein intact antibodies are proteolytically cleaved to generate $F(ab')_2$ fragments. These fragments are reduced in the presence of the dithiol com26S protease regulatory subunit 4g agent sodium arsenite to stabilize vicinal dithiols and prevent intermolecular disulfide formation. The Fab' fragments generated are then converted to thionitrobenzoate (TNB) derivatives. One of the Fab'-TNB derivatives is then reconverted to the Fab'-thiol by
 10 reduction with mercaptoethylamine and is mixed with an equimolar amount of the other Fab'-TNB derivative to form the bispecific antibody. The bispecific antibodies produced can be used as agents for the selective immobilization of enzymes.

Additionally, Fab' fragments can be directly recovered from *E. coli* and chemically coupled to form bispecific antibodies. Shalaby et al., *J. Exp. Med.* 175:217-225 (1992)
 15 describe the production of a fully humanized bispecific antibody $F(ab')_2$ molecule. Each Fab' fragment was separately secreted from *E. coli* and subjected to directed chemical coupling in vitro to form the bispecific antibody. The bispecific antibody thus formed was able to bind to cells overexpressing the ErbB2 receptor and normal human T cells, as well as trigger the lytic activity of human cytotoxic lymphocytes against human breast tumor targets.

20 Various techniques for making and isolating bispecific antibody fragments directly from recombinant cell culture have also been described. For example, bispecific antibodies have been produced using leucine zippers. Kostelny et al., *J. Immunol.* 148(5):1547-1553 (1992). The leucine zipper peptides from the Fos and Jun proteins were linked to the Fab' portions of two different antibodies by gene fusion. The antibody homodimers were reduced
 25 at the hinge region to form monomers and then re-oxidized to form the antibody heterodimers. This method can also be utilized for the production of antibody homodimers. The "diabody" technology described by Hollinger et al., *Proc. Natl. Acad. Sci. USA* 90:6444-6448 (1993) has provided an alternative mechanism for making bispecific antibody fragments. The fragments comprise a heavy-chain variable domain (V_H) connected to a light-chain variable domain (V_L)
 30 by a linker which is too short to allow pairing between the two domains on the same chain. Accordingly, the V_H and V_L domains of one fragment are forced to pair with the complementary V_L and V_H domains of another fragment, thereby forming two antigen-binding sites. Another strategy for making bispecific antibody fragments by the use of single-chain Fv (sFv) dimers has also been reported. See, Gruber et al., *J. Immunol.* 152:5368 (1994).

Antibodies with more than two valencies are contemplated. For example, trispecific antibodies can be prepared. Tutt et al., *J. Immunol.* 147:60 (1991).

Exemplary bispecific antibodies can bind to two different epitopes, at least one of which originates in the protein antigen of the invention. Alternatively, an anti-antigenic arm
 5 of an immunoglobulin molecule can be combined with an arm which binds to a triggering molecule on a leukocyte such as a T-cell receptor molecule (e.g. CD2, CD3, CD28, or B7), or Fc receptors for IgG (Fc γ R), such as Fc γ RI (CD64), Fc γ RII (CD32) and Fc γ RIII (CD16) so as to focus cellular defense mechanisms to the cell expressing the particular antigen. Bispecific
 10 antibodies can also be used to direct cytotoxic agents to cells which express a particular antigen. These antibodies possess an antigen-binding arm and an arm which binds a cytotoxic agent or a radionuclide chelator, such as EOTUBE, DPTA, DOTA, or TETA. Another bispecific antibody of interest binds the protein antigen described herein and further binds tissue factor (TF).

15 **Heteroconjugate Antibodies**

Heteroconjugate antibodies are also within the scope of the present invention. Heteroconjugate antibodies are composed of two covalently joined antibodies. Such antibodies have, for example, been proposed to target immune system cells to unwanted cells (U.S. Patent No. 4,676,980), and for treatment of HIV infection (WO 91/00360; WO
 20 92/200373; EP 03089). It is contemplated that the antibodies can be prepared in vitro using known methods in synthetic protein chemistry, including those involving crosslinking agents. For example, immunotoxins can be constructed using a disulfide exchange reaction or by forming a thioether bond. Examples of suitable reagents for this purpose include iminothiolate and methyl-4-mercaptobutyrimidate and those disclosed, for example, in U.S. Patent No.
 25 4,676,980.

Effector Function Engineering

It can be desirable to modify the antibody of the invention with respect to effector function, so as to enhance, e.g., the effectiveness of the antibody in treating cancer. For
 30 example, cysteine residue(s) can be introduced into the Fc region, thereby allowing interchain disulfide bond formation in this region. The homodimeric antibody thus generated can have improved internalization capability and/or increased complement-mediated cell killing and antibody-dependent cellular cytotoxicity (ADCC). See Caron et al., *J. Exp Med.*, 176: 1191-1195 (1992) and Shopes, *J. Immunol.*, 148: 2918-2922 (1992). Homodimeric antibodies with

enhanced anti-tumor activity can also be prepared using heterobifunctional cross-linkers as described in Wolff et al. Cancer Research, 53: 2560-2565 (1993). Alternatively, an antibody can be engineered that has dual Fc regions and can thereby have enhanced complement lysis and ADCC capabilities. See Stevenson et al., Anti-Cancer Drug Design, 3: 219-230 (1989).

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Immunoconjugates

The invention also pertains to immunoconjugates comprising an antibody conjugated to a cytotoxic agent such as a chemotherapeutic agent, toxin (e.g., an enzymatically active toxin of bacterial, fungal, plant, or animal origin, or fragments thereof), or a radioactive isotope (i.e., a radioconjugate).

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Chemotherapeutic agents useful in the generation of such immunoconjugates have been described above. Enzymatically active toxins and fragments thereof that can be used include diphtheria A chain, nonbinding active fragments of diphtheria toxin, exotoxin A chain (from *Pseudomonas aeruginosa*), ricin A chain, abrin A chain, modeccin A chain, alpha-sarcin, Aleurites fordii proteins, dianthin proteins, Phytolaca americana proteins (PAPI, PAPII, and PAP-S), momordica charantia inhibitor, curcin, crotin, sapaonaria officinalis inhibitor, gelonin, mitogellin, restrictocin, phenomycin, enomycin, and the tricothecenes. A variety of radionuclides are available for the production of radioconjugated antibodies. Examples include ^{212}Bi , ^{131}I , ^{131}In , ^{90}Y , and ^{186}Re .

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Conjugates of the antibody and cytotoxic agent are made using a variety of bifunctional protein-coupling agents such as N-succinimidyl-3-(2-pyridyldithiol) propionate (SPDP), iminothiolane (IT), bifunctional derivatives of imidoesters (such as dimethyl adipimide HCL), active esters (such as disuccinimidyl suberate), aldehydes (such as glutaraldehyde), bis-azido compounds (such as bis (p-azidobenzoyl) hexanediamine), bis-diazonium derivatives (such as bis-(p-diazoniumbenzoyl)-ethylenediamine), diisocyanates (such as tolyene 2,6-diisocyanate), and bis-active fluorine compounds (such as 1,5-difluoro-2,4-dinitrobenzene). For example, a ricin immunotoxin can be prepared as described in Vitetta et al., Science, 238: 1098 (1987). Carbon-14-labeled 1-isothiocyanatobenzyl-3-methyldiethylene triaminepentaacetic acid (MX-DTPA) is an exemplary chelating agent for conjugation of radionucleotide to the antibody. See WO94/11026.

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In another embodiment, the antibody can be conjugated to a "receptor" (such as streptavidin) for utilization in tumor pretargeting wherein the antibody-receptor conjugate is administered to the patient, followed by removal of unbound conjugate from the circulation

using a clearing agent and then administration of a "ligand" (e.g., avidin) that is in turn conjugated to a cytotoxic agent.

In one embodiment, methods for the screening of antibodies that possess the desired specificity include, but are not limited to, enzyme-linked immunosorbent assay (ELISA) and other immunologically-mediated techniques known within the art. In a specific embodiment, selection of antibodies that are specific to a particular domain of an NOVX protein is facilitated by generation of hybridomas that bind to the fragment of an NOVX protein possessing such a domain. Thus, antibodies that are specific for a desired domain within an NOVX protein, or derivatives, fragments, analogs or homologs thereof, are also provided herein.

Anti-NOVX antibodies may be used in methods known within the art relating to the localization and/or quantitation of an NOVX protein (e.g., for use in measuring levels of the NOVX protein within appropriate physiological samples, for use in diagnostic methods, for use in imaging the protein, and the like). In a given embodiment, antibodies for NOVX proteins, or derivatives, fragments, analogs or homologs thereof, that contain the antibody derived binding domain, are utilized as pharmacologically-active compounds (hereinafter "Therapeutics").

An anti-NOVX antibody (e.g., monoclonal antibody) can be used to isolate an NOVX polypeptide by standard techniques, such as affinity chromatography or immunoprecipitation. An anti-NOVX antibody can facilitate the purification of natural NOVX polypeptide from cells and of recombinantly-produced NOVX polypeptide expressed in host cells. Moreover, an anti-NOVX antibody can be used to detect NOVX protein (e.g., in a cellular lysate or cell supernatant) in order to evaluate the abundance and pattern of expression of the NOVX protein. Anti-NOVX antibodies can be used diagnostically to monitor protein levels in tissue as part of a clinical testing procedure, e.g., to, for example, determine the efficacy of a given treatment regimen. Detection can be facilitated by coupling (i.e., physically linking) the antibody to a detectable substance. Examples of detectable substances include various enzymes, prosthetic groups, fluorescent materials, luminescent materials, bioluminescent materials, and radioactive materials. Examples of suitable enzymes include horseradish peroxidase, alkaline phosphatase, β -galactosidase, or acetylcholinesterase; examples of suitable prosthetic group complexes include streptavidin/biotin and avidin/biotin; examples of suitable fluorescent materials include umbelliferone, fluorescein, fluorescein isothiocyanate, rhodamine, dichlorotriazinylamine fluorescein, dansyl chloride or phycoerythrin; an example of a luminescent material includes luminol; examples of bioluminescent materials include

luciferase, luciferin, and aequorin, and examples of suitable radioactive material include ^{125}I , ^{131}I , ^{35}S or ^3H .

NOVX Recombinant Expression Vectors and Host Cells

5 Another aspect of the invention pertains to vectors, preferably expression vectors, containing a nucleic acid encoding an NOVX protein, or derivatives, fragments, analogs or homologs thereof. As used herein, the term "vector" refers to a nucleic acid molecule capable of transporting another nucleic acid to which it has been linked. One type of vector is a "plasmid", which refers to a circular double stranded DNA loop into which additional DNA
10 segments can be ligated. Another type of vector is a viral vector, wherein additional DNA segments can be ligated into the viral genome. Certain vectors are capable of autonomous replication in a host cell into which they are introduced (*e.g.*, bacterial vectors having a bacterial origin of replication and episomal mammalian vectors). Other vectors (*e.g.*, non-episomal mammalian vectors) are integrated into the genome of a host cell upon
15 introduction into the host cell, and thereby are replicated along with the host genome. Moreover, certain vectors are capable of directing the expression of genes to which they are operatively-linked. Such vectors are referred to herein as "expression vectors". In general, expression vectors of utility in recombinant DNA techniques are often in the form of plasmids. In the present specification, "plasmid" and "vector" can be used interchangeably as the
20 plasmid is the most commonly used form of vector. However, the invention is intended to include such other forms of expression vectors, such as viral vectors (*e.g.*, replication defective retroviruses, adenoviruses and adeno-associated viruses), which serve equivalent functions.

The recombinant expression vectors of the invention comprise a nucleic acid of the invention in a form suitable for expression of the nucleic acid in a host cell, which means that
25 the recombinant expression vectors include one or more regulatory sequences, selected on the basis of the host cells to be used for expression, that is operatively-linked to the nucleic acid sequence to be expressed. Within a recombinant expression vector, "operably-linked" is intended to mean that the nucleotide sequence of interest is linked to the regulatory sequence(s) in a manner that allows for expression of the nucleotide sequence (*e.g.*, in an *in vitro* transcription/translation system or in a host cell when the vector is introduced into the
30 host cell).

The term "regulatory sequence" is intended to include promoters, enhancers and other expression control elements (*e.g.*, polyadenylation signals). Such regulatory sequences are described, for example, in Goeddel, GENE EXPRESSION TECHNOLOGY: METHODS IN

ENZYMOLOGY 185, Academic Press, San Diego, Calif. (1990). Regulatory sequences include those that direct constitutive expression of a nucleotide sequence in many types of host cell and those that direct expression of the nucleotide sequence only in certain host cells (*e.g.*, tissue-specific regulatory sequences). It will be appreciated by those skilled in the art that the design of the expression vector can depend on such factors as the choice of the host cell to be transformed, the level of expression of protein desired, etc. The expression vectors of the invention can be introduced into host cells to thereby produce proteins or peptides, including fusion proteins or peptides, encoded by nucleic acids as described herein (*e.g.*, NOVX proteins, mutant forms of NOVX proteins, fusion proteins, etc.).

The recombinant expression vectors of the invention can be designed for expression of NOVX proteins in prokaryotic or eukaryotic cells. For example, NOVX proteins can be expressed in bacterial cells such as *Escherichia coli*, insect cells (using baculovirus expression vectors) yeast cells or mammalian cells. Suitable host cells are discussed further in Goeddel, GENE EXPRESSION TECHNOLOGY: METHODS IN ENZYMOLOGY 185, Academic Press, San Diego, Calif. (1990). Alternatively, the recombinant expression vector can be transcribed and translated *in vitro*, for example using T7 promoter regulatory sequences and T7 polymerase.

Expression of proteins in prokaryotes is most often carried out in *Escherichia coli* with vectors containing constitutive or inducible promoters directing the expression of either fusion or non-fusion proteins. Fusion vectors add a number of amino acids to a protein encoded therein, usually to the amino terminus of the recombinant protein. Such fusion vectors typically serve three purposes: (i) to increase expression of recombinant protein; (ii) to increase the solubility of the recombinant protein; and (iii) to aid in the purification of the recombinant protein by acting as a ligand in affinity purification. Often, in fusion expression vectors, a proteolytic cleavage site is introduced at the junction of the fusion moiety and the recombinant protein to enable separation of the recombinant protein from the fusion moiety subsequent to purification of the fusion protein. Such enzymes, and their cognate recognition sequences, include Factor Xa, thrombin and enterokinase. Typical fusion expression vectors include pGEX (Pharmacia Biotech Inc; Smith and Johnson, 1988. *Gene* 67: 31-40), pMAL (New England Biolabs, Beverly, Mass.) and pRIT5 (Pharmacia, Piscataway, N.J.) that fuse glutathione S-transferase (GST), maltose E binding protein, or protein A, respectively, to the target recombinant protein.

Examples of suitable inducible non-fusion *E. coli* expression vectors include pTrc (Amrann *et al.*, (1988) *Gene* 69:301-315) and pET 11d (Studier *et al.*, GENE EXPRESSION

TECHNOLOGY: METHODS IN ENZYMOLOGY 185, Academic Press, San Diego, Calif. (1990) 60-89).

One strategy to maximize recombinant protein expression in *E. coli* is to express the protein in a host bacteria with an impaired capacity to proteolytically cleave the recombinant protein. See, e.g., Gottesman, GENE EXPRESSION TECHNOLOGY: METHODS IN ENZYMOLOGY 185, Academic Press, San Diego, Calif. (1990) 119-128. Another strategy is to alter the nucleic acid sequence of the nucleic acid to be inserted into an expression vector so that the individual codons for each amino acid are those preferentially utilized in *E. coli* (see, e.g., Wada, *et al.*, 1992. *Nucl. Acids Res.* 20: 2111-2118). Such alteration of nucleic acid sequences of the invention can be carried out by standard DNA synthesis techniques.

In another embodiment, the NOVX expression vector is a yeast expression vector. Examples of vectors for expression in yeast *Saccharomyces cerevisiae* include pYepSec1 (Baldari, *et al.*, 1987. *EMBO J.* 6: 229-234), pMFa (Kurjan and Herskowitz, 1982. *Cell* 30: 933-943), pJRY88 (Schultz *et al.*, 1987. *Gene* 54: 113-123), pYES2 (Invitrogen Corporation, San Diego, Calif.), and picZ (Invitrogen Corp, San Diego, Calif.).

Alternatively, NOVX can be expressed in insect cells using baculovirus expression vectors. Baculovirus vectors available for expression of proteins in cultured insect cells (e.g., SF9 cells) include the pAc series (Smith, *et al.*, 1983. *Mol. Cell. Biol.* 3: 2156-2165) and the pVL series (Lucklow and Summers, 1989. *Virology* 170: 31-39).

In yet another embodiment, a nucleic acid of the invention is expressed in mammalian cells using a mammalian expression vector. Examples of mammalian expression vectors include pCDM8 (Seed, 1987. *Nature* 329: 840) and pMT2PC (Kaufman, *et al.*, 1987. *EMBO J.* 6: 187-195). When used in mammalian cells, the expression vector's control functions are often provided by viral regulatory elements. For example, commonly used promoters are derived from polyoma, adenovirus 2, cytomegalovirus, and simian virus 40. For other suitable expression systems for both prokaryotic and eukaryotic cells see, e.g., Chapters 16 and 17 of Sambrook, *et al.*, MOLECULAR CLONING: A LABORATORY MANUAL. 2nd ed., Cold Spring Harbor Laboratory, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., 1989.

In another embodiment, the recombinant mammalian expression vector is capable of directing expression of the nucleic acid preferentially in a particular cell type (e.g., tissue-specific regulatory elements are used to express the nucleic acid). Tissue-specific regulatory elements are known in the art. Non-limiting examples of suitable tissue-specific promoters include the albumin promoter (liver-specific; Pinkert, *et al.*, 1987. *Genes Dev.* 1: 268-277), lymphoid-specific promoters (Calame and Eaton, 1988. *Adv. Immunol.* 43:

235-275), in particular promoters of T cell receptors (Winoto and Baltimore, 1989. *EMBO J.* 8: 729-733) and immunoglobulins (Banerji, *et al.*, 1983. *Cell* 33: 729-740; Queen and Baltimore, 1983. *Cell* 33: 741-748), neuron-specific promoters (*e.g.*, the neurofilament promoter; Byrne and Ruddle, 1989. *Proc. Natl. Acad. Sci. USA* 86: 5473-5477),
5 pancreas-specific promoters (Edlund, *et al.*, 1985. *Science* 230: 912-916), and mammary gland-specific promoters (*e.g.*, milk whey promoter; U.S. Pat. No. 4,873,316 and European Application Publication No. 264,166). Developmentally-regulated promoters are also encompassed, *e.g.*, the murine hox promoters (Kessel and Gruss, 1990. *Science* 249: 374-379) and the α -fetoprotein promoter (Campes and Tilghman, 1989. *Genes Dev.* 3: 537-546).

10 The invention further provides a recombinant expression vector comprising a DNA molecule of the invention cloned into the expression vector in an antisense orientation. That is, the DNA molecule is operatively-linked to a regulatory sequence in a manner that allows for expression (by transcription of the DNA molecule) of an RNA molecule that is antisense to NOVX mRNA. Regulatory sequences operatively linked to a nucleic acid cloned in the
15 antisense orientation can be chosen that direct the continuous expression of the antisense RNA molecule in a variety of cell types, for instance viral promoters and/or enhancers, or regulatory sequences can be chosen that direct constitutive, tissue specific or cell type specific expression of antisense RNA. The antisense expression vector can be in the form of a recombinant plasmid, phagemid or attenuated virus in which antisense nucleic acids are produced under the
20 control of a high efficiency regulatory region, the activity of which can be determined by the cell type into which the vector is introduced. For a discussion of the regulation of gene expression using antisense genes *see, e.g.*, Weintraub, *et al.*, "Antisense RNA as a molecular tool for genetic analysis," *Reviews-Trends in Genetics*, Vol. 1(1) 1986.

Another aspect of the invention pertains to host cells into which a recombinant
25 expression vector of the invention has been introduced. The terms "host cell" and "recombinant host cell" are used interchangeably herein. It is understood that such terms refer not only to the particular subject cell but also to the progeny or potential progeny of such a cell. Because certain modifications may occur in succeeding generations due to either mutation or environmental influences, such progeny may not, in fact, be identical to the parent
30 cell, but are still included within the scope of the term as used herein.

A host cell can be any prokaryotic or eukaryotic cell. For example, NOVX protein can be expressed in bacterial cells such as *E. coli*, insect cells, yeast or mammalian cells (such as Chinese hamster ovary cells (CHO) or COS cells). Other suitable host cells are known to those skilled in the art.

Vector DNA can be introduced into prokaryotic or eukaryotic cells via conventional transformation or transfection techniques. As used herein, the terms "transformation" and "transfection" are intended to refer to a variety of art-recognized techniques for introducing foreign nucleic acid (*e.g.*, DNA) into a host cell, including calcium phosphate or calcium chloride co-precipitation, DEAE-dextran-mediated transfection, lipofection, or electroporation. Suitable methods for transforming or transfecting host cells can be found in Sambrook, *et al.* (MOLECULAR CLONING: A LABORATORY MANUAL, 2nd ed., Cold Spring Harbor Laboratory, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., 1989), and other laboratory manuals.

For stable transfection of mammalian cells, it is known that, depending upon the expression vector and transfection technique used, only a small fraction of cells may integrate the foreign DNA into their genome. In order to identify and select these integrants, a gene that encodes a selectable marker (*e.g.*, resistance to antibiotics) is generally introduced into the host cells along with the gene of interest. Various selectable markers include those that confer resistance to drugs, such as G418, hygromycin and methotrexate. Nucleic acid encoding a selectable marker can be introduced into a host cell on the same vector as that encoding NOVX or can be introduced on a separate vector. Cells stably transfected with the introduced nucleic acid can be identified by drug selection (*e.g.*, cells that have incorporated the selectable marker gene will survive, while the other cells die).

A host cell of the invention, such as a prokaryotic or eukaryotic host cell in culture, can be used to produce (*i.e.*, express) NOVX protein. Accordingly, the invention further provides methods for producing NOVX protein using the host cells of the invention. In one embodiment, the method comprises culturing the host cell of invention (into which a recombinant expression vector encoding NOVX protein has been introduced) in a suitable medium such that NOVX protein is produced. In another embodiment, the method further comprises isolating NOVX protein from the medium or the host cell.

Transgenic NOVX Animals

The host cells of the invention can also be used to produce non-human transgenic animals. For example, in one embodiment, a host cell of the invention is a fertilized oocyte or an embryonic stem cell into which NOVX protein-coding sequences have been introduced. Such host cells can then be used to create non-human transgenic animals in which exogenous NOVX sequences have been introduced into their genome or homologous recombinant animals in which endogenous NOVX sequences have been altered. Such animals are useful

for studying the function and/or activity of NOVX protein and for identifying and/or evaluating modulators of NOVX protein activity. As used herein, a "transgenic animal" is a non-human animal, preferably a mammal, more preferably a rodent such as a rat or mouse, in which one or more of the cells of the animal includes a transgene. Other examples of
5 transgenic animals include non-human primates, sheep, dogs, cows, goats, chickens, amphibians, etc. A transgene is exogenous DNA that is integrated into the genome of a cell from which a transgenic animal develops and that remains in the genome of the mature animal, thereby directing the expression of an encoded gene product in one or more cell types or tissues of the transgenic animal. As used herein, a "homologous recombinant animal" is a
10 non-human animal, preferably a mammal, more preferably a mouse, in which an endogenous NOVX gene has been altered by homologous recombination between the endogenous gene and an exogenous DNA molecule introduced into a cell of the animal, *e.g.*, an embryonic cell of the animal, prior to development of the animal.

A transgenic animal of the invention can be created by introducing NOVX-encoding
15 nucleic acid into the male pronuclei of a fertilized oocyte (*e.g.*, by microinjection, retroviral infection) and allowing the oocyte to develop in a pseudopregnant female foster animal. The human NOVX cDNA sequences SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, and 217 can be introduced as a transgene into the genome of a non-human animal. Alternatively, a non-human homologue of the human NOVX gene, such as a mouse NOVX
20 gene, can be isolated based on hybridization to the human NOVX cDNA (described further *supra*) and used as a transgene. Intronic sequences and polyadenylation signals can also be included in the transgene to increase the efficiency of expression of the transgene. A tissue-specific regulatory sequence(s) can be operably-linked to the NOVX transgene to direct expression of NOVX protein to particular cells. Methods for generating transgenic animals
25 via embryo manipulation and microinjection, particularly animals such as mice, have become conventional in the art and are described, for example, in U.S. Patent Nos. 4,736,866; 4,870,009; and 4,873,191; and Hogan, 1986. In: MANIPULATING THE MOUSE EMBRYO, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y. Similar methods are used for production of other transgenic animals. A transgenic founder animal can be identified based
30 upon the presence of the NOVX transgene in its genome and/or expression of NOVX mRNA in tissues or cells of the animals. A transgenic founder animal can then be used to breed additional animals carrying the transgene. Moreover, transgenic animals carrying a transgene-encoding NOVX protein can further be bred to other transgenic animals carrying other transgenes.

To create a homologous recombinant animal, a vector is prepared which contains at least a portion of an NOVX gene into which a deletion, addition or substitution has been introduced to thereby alter, *e.g.*, functionally disrupt, the NOVX gene. The NOVX gene can be a human gene (*e.g.*, the cDNA of SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, and 217), but more preferably, is a non-human homologue of a human NOVX gene. For example, a mouse homologue of human NOVX gene of SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, and 217 can be used to construct a homologous recombination vector suitable for altering an endogenous NOVX gene in the mouse genome. In one embodiment, the vector is designed such that, upon homologous recombination, the endogenous NOVX gene is functionally disrupted (*i.e.*, no longer encodes a functional protein; also referred to as a "knock out" vector).

Alternatively, the vector can be designed such that, upon homologous recombination, the endogenous NOVX gene is mutated or otherwise altered but still encodes functional protein (*e.g.*, the upstream regulatory region can be altered to thereby alter the expression of the endogenous NOVX protein). In the homologous recombination vector, the altered portion of the NOVX gene is flanked at its 5'- and 3'-termini by additional nucleic acid of the NOVX gene to allow for homologous recombination to occur between the exogenous NOVX gene carried by the vector and an endogenous NOVX gene in an embryonic stem cell. The additional flanking NOVX nucleic acid is of sufficient length for successful homologous recombination with the endogenous gene. Typically, several kilobases of flanking DNA (both at the 5'- and 3'-termini) are included in the vector. *See, e.g.*, Thomas, *et al.*, 1987. *Cell* 51: 503 for a description of homologous recombination vectors. The vector is then introduced into an embryonic stem cell line (*e.g.*, by electroporation) and cells in which the introduced NOVX gene has homologously-recombined with the endogenous NOVX gene are selected. *See, e.g.*, Li, *et al.*, 1992. *Cell* 69: 915.

The selected cells are then injected into a blastocyst of an animal (*e.g.*, a mouse) to form aggregation chimeras. *See, e.g.*, Bradley, 1987. In: TERATOCARCINOMAS AND EMBRYONIC STEM CELLS: A PRACTICAL APPROACH, Robertson, ed. IRL, Oxford, pp. 113-152. A chimeric embryo can then be implanted into a suitable pseudopregnant female foster animal and the embryo brought to term. Progeny harboring the homologously-recombined DNA in their germ cells can be used to breed animals in which all cells of the animal contain the homologously-recombined DNA by germline transmission of the transgene. Methods for constructing homologous recombination vectors and homologous recombinant animals are

described further in Bradley, 1991. *Curr. Opin. Biotechnol.* 2: 823-829; PCT International Publication Nos.: WO 90/11354; WO 91/01140; WO 92/0968; and WO 93/04169.

In another embodiment, transgenic non-humans animals can be produced that contain selected systems that allow for regulated expression of the transgene. One example of such a system is the cre/loxP recombinase system of bacteriophage P1. For a description of the cre/loxP recombinase system, See, e.g., Lakso, *et al.*, 1992. *Proc. Natl. Acad. Sci. USA* 89: 6232-6236. Another example of a recombinase system is the FLP recombinase system of *Saccharomyces cerevisiae*. See, O'Gorman, *et al.*, 1991. *Science* 251:1351-1355. If a cre/loxP recombinase system is used to regulate expression of the transgene, animals containing transgenes encoding both the Cre recombinase and a selected protein are required. Such animals can be provided through the construction of "double" transgenic animals, e.g., by mating two transgenic animals, one containing a transgene encoding a selected protein and the other containing a transgene encoding a recombinase.

Clones of the non-human transgenic animals described herein can also be produced according to the methods described in Wilmut, *et al.*, 1997. *Nature* 385: 810-813. In brief, a cell (e.g., a somatic cell) from the transgenic animal can be isolated and induced to exit the growth cycle and enter G₀ phase. The quiescent cell can then be fused, e.g., through the use of electrical pulses, to an enucleated oocyte from an animal of the same species from which the quiescent cell is isolated. The reconstructed oocyte is then cultured such that it develops to morula or blastocyte and then transferred to pseudopregnant female foster animal. The offspring borne of this female foster animal will be a clone of the animal from which the cell (e.g., the somatic cell) is isolated.

Pharmaceutical Compositions

The NOVX nucleic acid molecules, NOVX proteins, and anti-NOVX antibodies (also referred to herein as "active compounds") of the invention, and derivatives, fragments, analogs and homologs thereof, can be incorporated into pharmaceutical compositions suitable for administration. Such compositions typically comprise the nucleic acid molecule, protein, or antibody and a pharmaceutically acceptable carrier. As used herein, "pharmaceutically acceptable carrier" is intended to include any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like, compatible with pharmaceutical administration. Suitable carriers are described in the most recent edition of Remington's Pharmaceutical Sciences, a standard reference text in the field, which is incorporated herein by reference. Preferred examples of such carriers or diluents

include, but are not limited to, water, saline, finger's solutions, dextrose solution, and 5% human serum albumin. Liposomes and non-aqueous vehicles such as fixed oils may also be used. The use of such media and agents for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active compound, use thereof in the compositions is contemplated. Supplementary active compounds can also be incorporated into the compositions.

A pharmaceutical composition of the invention is formulated to be compatible with its intended route of administration. Examples of routes of administration include parenteral, *e.g.*, intravenous, intradermal, subcutaneous, oral (*e.g.*, inhalation), transdermal (*i.e.*, topical), transmucosal, and rectal administration. Solutions or suspensions used for parenteral, intradermal, or subcutaneous application can include the following components: a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid (EDTA); buffers such as acetates, citrates or phosphates, and agents for the adjustment of tonicity such as sodium chloride or dextrose. The pH can be adjusted with acids or bases, such as hydrochloric acid or sodium hydroxide. The parenteral preparation can be enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic.

Pharmaceutical compositions suitable for injectable use include sterile aqueous solutions (where water soluble) or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersion. For intravenous administration, suitable carriers include physiological saline, bacteriostatic water, Cremophor EL™ (BASF, Parsippany, N.J.) or phosphate buffered saline (PBS). In all cases, the composition must be sterile and should be fluid to the extent that easy syringeability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. Prevention of the action of microorganisms can be achieved by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, ascorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents,

for example, sugars, polyalcohols such as manitol, sorbitol, sodium chloride in the composition. Prolonged absorption of the injectable compositions can be brought about by including in the composition an agent which delays absorption, for example, aluminum monostearate and gelatin.

5 Sterile injectable solutions can be prepared by incorporating the active compound (*e.g.*, an NOVX protein or anti-NOVX antibody) in the required amount in an appropriate solvent with one or a combination of ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the active compound into a sterile vehicle that contains a basic dispersion medium and the required other ingredients from
10 those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, methods of preparation are vacuum drying and freeze-drying that yields a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof.

Oral compositions generally include an inert diluent or an edible carrier. They can be
15 enclosed in gelatin capsules or compressed into tablets. For the purpose of oral therapeutic administration, the active compound can be incorporated with excipients and used in the form of tablets, troches, or capsules. Oral compositions can also be prepared using a fluid carrier for use as a mouthwash, wherein the compound in the fluid carrier is applied orally and swished and expectorated or swallowed. Pharmaceutically compatible binding agents, and/or
20 adjuvant materials can be included as part of the composition. The tablets, pills, capsules, troches and the like can contain any of the following ingredients, or compounds of a similar nature: a binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose, a disintegrating agent such as alginic acid, Primogel, or corn starch; a lubricant such as magnesium stearate or Sterotes; a glidant such as colloidal silicon dioxide; a
25 sweetening agent such as sucrose or saccharin; or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring.

For administration by inhalation, the compounds are delivered in the form of an aerosol spray from pressured container or dispenser which contains a suitable propellant, *e.g.*, a gas such as carbon dioxide, or a nebulizer.

30 Systemic administration can also be by transmucosal or transdermal means. For transmucosal or transdermal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art, and include, for example, for transmucosal administration, detergents, bile salts, and fusidic acid derivatives. Transmucosal administration can be accomplished through the use of nasal sprays

or suppositories. For transdermal administration, the active compounds are formulated into ointments, salves, gels, or creams as generally known in the art.

The compounds can also be prepared in the form of suppositories (*e.g.*, with conventional suppository bases such as cocoa butter and other glycerides) or retention enemas for rectal delivery.

In one embodiment, the active compounds are prepared with carriers that will protect the compound against rapid elimination from the body, such as a controlled release formulation, including implants and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid. Methods for preparation of such formulations will be apparent to those skilled in the art. The materials can also be obtained commercially from Alza Corporation and Nova Pharmaceuticals, Inc. Liposomal suspensions (including liposomes targeted to infected cells with monoclonal antibodies to viral antigens) can also be used as pharmaceutically acceptable carriers. These can be prepared according to methods known to those skilled in the art, for example, as described in U.S. Patent No. 4,522,811.

It is especially advantageous to formulate oral or parenteral compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the subject to be treated; each unit containing a predetermined quantity of active compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specification for the dosage unit forms of the invention are dictated by and directly dependent on the unique characteristics of the active compound and the particular therapeutic effect to be achieved, and the limitations inherent in the art of compounding such an active compound for the treatment of individuals.

The nucleic acid molecules of the invention can be inserted into vectors and used as gene therapy vectors. Gene therapy vectors can be delivered to a subject by, for example, intravenous injection, local administration (*see, e.g.*, U.S. Patent No. 5,328,470) or by stereotactic injection (*see, e.g.*, Chen, *et al.*, 1994. *Proc. Natl. Acad. Sci. USA* 91: 3054-3057). The pharmaceutical preparation of the gene therapy vector can include the gene therapy vector in an acceptable diluent, or can comprise a slow release matrix in which the gene delivery vehicle is imbedded. Alternatively, where the complete gene delivery vector can be produced intact from recombinant cells, *e.g.*, retroviral vectors, the pharmaceutical preparation can include one or more cells that produce the gene delivery system.

The pharmaceutical compositions can be included in a container, pack, or dispenser together with instructions for administration.

Screening and Detection Methods

The isolated nucleic acid molecules of the invention can be used to express NOVX protein (*e.g.*, via a recombinant expression vector in a host cell in gene therapy applications), to detect NOVX mRNA (*e.g.*, in a biological sample) or a genetic lesion in an NOVX gene, and to modulate NOVX activity, as described further, below. In addition, the NOVX proteins can be used to screen drugs or compounds that modulate the NOVX protein activity or expression as well as to treat disorders characterized by insufficient or excessive production of NOVX protein or production of NOVX protein forms that have decreased or aberrant activity compared to NOVX wild-type protein (*e.g.*; diabetes (regulates insulin release); obesity (binds and transport lipids); metabolic disturbances associated with obesity, the metabolic syndrome X as well as anorexia and wasting disorders associated with chronic diseases and various cancers, and infectious disease (possesses anti-microbial activity) and the various dyslipidemias. In addition, the anti-NOVX antibodies of the invention can be used to detect and isolate NOVX proteins and modulate NOVX activity. In yet a further aspect, the invention can be used in methods to influence appetite, absorption of nutrients and the disposition of metabolic substrates in both a positive and negative fashion.

The invention further pertains to novel agents identified by the screening assays described herein and uses thereof for treatments as described, *supra*.

Screening Assays

The invention provides a method (also referred to herein as a "screening assay") for identifying modulators, *i.e.*, candidate or test compounds or agents (*e.g.*, peptides, peptidomimetics, small molecules or other drugs) that bind to NOVX proteins or have a stimulatory or inhibitory effect on, *e.g.*, NOVX protein expression or NOVX protein activity. The invention also includes compounds identified in the screening assays described herein.

In one embodiment, the invention provides assays for screening candidate or test compounds which bind to or modulate the activity of the membrane-bound form of an NOVX protein or polypeptide or biologically-active portion thereof. The test compounds of the invention can be obtained using any of the numerous approaches in combinatorial library methods known in the art, including: biological libraries; spatially addressable parallel solid phase or solution phase libraries; synthetic library methods requiring deconvolution; the

“one-bead one-compound” library method; and synthetic library methods using affinity chromatography selection. The biological library approach is limited to peptide libraries, while the other four approaches are applicable to peptide, non-peptide oligomer or small molecule libraries of compounds. *See, e.g., Lam, 1997. Anticancer Drug Design* 12: 145.

5 A "small molecule" as used herein, is meant to refer to a composition that has a molecular weight of less than about 5 kD and most preferably less than about 4 kD. Small molecules can be, *e.g.,* nucleic acids, peptides, polypeptides, peptidomimetics, carbohydrates, lipids or other organic or inorganic molecules. Libraries of chemical and/or biological mixtures, such as fungal, bacterial, or algal extracts, are known in the art and can be screened
10 with any of the assays of the invention.

Examples of methods for the synthesis of molecular libraries can be found in the art, for example in: DeWitt, *et al.*, 1993. *Proc. Natl. Acad. Sci. U.S.A.* 90: 6909; Erb, *et al.*, 1994. *Proc. Natl. Acad. Sci. U.S.A.* 91: 11422; Zuckermann, *et al.*, 1994. *J. Med. Chem.* 37: 2678; Cho, *et al.*, 1993. *Science* 261: 1303; Carrell, *et al.*, 1994. *Angew. Chem. Int. Ed. Engl.* 33:
15 2059; Carell, *et al.*, 1994. *Angew. Chem. Int. Ed. Engl.* 33: 2061; and Gallop, *et al.*, 1994. *J. Med. Chem.* 37: 1233.

Libraries of compounds may be presented in solution (*e.g.,* Houghten, 1992. *Biotechniques* 13: 412-421), or on beads (Lam, 1991. *Nature* 354: 82-84), on chips (Fodor, 1993. *Nature* 364: 555-556), bacteria (Ladner, U.S. Patent No. 5,223,409), spores (Ladner,
20 U.S. Patent 5,233,409), plasmids (Cull, *et al.*, 1992. *Proc. Natl. Acad. Sci. USA* 89: 1865-1869) or on phage (Scott and Smith, 1990. *Science* 249: 386-390; Devlin, 1990. *Science* 249: 404-406; Cwirla, *et al.*, 1990. *Proc. Natl. Acad. Sci. U.S.A.* 87: 6378-6382; Felici, 1991. *J. Mol. Biol.* 222: 301-310; Ladner, U.S. Patent No. 5,233,409.).

In one embodiment, an assay is a cell-based assay in which a cell which expresses a
25 membrane-bound form of NOVX protein, or a biologically-active portion thereof, on the cell surface is contacted with a test compound and the ability of the test compound to bind to an NOVX protein determined. The cell, for example, can of mammalian origin or a yeast cell. Determining the ability of the test compound to bind to the NOVX protein can be accomplished, for example, by coupling the test compound with a radioisotope or enzymatic
30 label such that binding of the test compound to the NOVX protein or biologically-active portion thereof can be determined by detecting the labeled compound in a complex. For example, test compounds can be labeled with ¹²⁵I, ³⁵S, ¹⁴C, or ³H, either directly or indirectly, and the radioisotope detected by direct counting of radioemission or by scintillation counting. Alternatively, test compounds can be enzymatically-labeled with, for example, horseradish

peroxidase, alkaline phosphatase, or luciferase, and the enzymatic label detected by determination of conversion of an appropriate substrate to product. In one embodiment, the assay comprises contacting a cell which expresses a membrane-bound form of NOVX protein, or a biologically-active portion thereof, on the cell surface with a known compound which
5 binds NOVX to form an assay mixture, contacting the assay mixture with a test compound, and determining the ability of the test compound to interact with an NOVX protein, wherein determining the ability of the test compound to interact with an NOVX protein comprises determining the ability of the test compound to preferentially bind to NOVX protein or a biologically-active portion thereof as compared to the known compound.

10 In another embodiment, an assay is a cell-based assay comprising contacting a cell expressing a membrane-bound form of NOVX protein, or a biologically-active portion thereof, on the cell surface with a test compound and determining the ability of the test compound to modulate (*e.g.*, stimulate or inhibit) the activity of the NOVX protein or biologically-active portion thereof. Determining the ability of the test compound to modulate the activity of
15 NOVX or a biologically-active portion thereof can be accomplished, for example, by determining the ability of the NOVX protein to bind to or interact with an NOVX target molecule. As used herein, a "target molecule" is a molecule with which an NOVX protein binds or interacts in nature, for example, a molecule on the surface of a cell which expresses an NOVX interacting protein, a molecule on the surface of a second cell, a molecule in the
20 extracellular milieu, a molecule associated with the internal surface of a cell membrane or a cytoplasmic molecule. An NOVX target molecule can be a non-NOVX molecule or an NOVX protein or polypeptide of the invention. In one embodiment, an NOVX target molecule is a component of a signal transduction pathway that facilitates transduction of an extracellular signal (*e.g.* a signal generated by binding of a compound to a membrane-bound
25 NOVX molecule) through the cell membrane and into the cell. The target, for example, can be a second intercellular protein that has catalytic activity or a protein that facilitates the association of downstream signaling molecules with NOVX.

Determining the ability of the NOVX protein to bind to or interact with an NOVX target molecule can be accomplished by one of the methods described above for determining
30 direct binding. In one embodiment, determining the ability of the NOVX protein to bind to or interact with an NOVX target molecule can be accomplished by determining the activity of the target molecule. For example, the activity of the target molecule can be determined by detecting induction of a cellular second messenger of the target (*i.e.* intracellular Ca^{2+} , diacylglycerol, IP_3 , etc.), detecting catalytic/enzymatic activity of the target an appropriate

substrate, detecting the induction of a reporter gene (comprising an NOVX-responsive regulatory element operatively linked to a nucleic acid encoding a detectable marker, *e.g.*, luciferase), or detecting a cellular response, for example, cell survival, cellular differentiation, or cell proliferation.

5 In yet another embodiment, an assay of the invention is a cell-free assay comprising contacting an NOVX protein or biologically-active portion thereof with a test compound and determining the ability of the test compound to bind to the NOVX protein or biologically-active portion thereof. Binding of the test compound to the NOVX protein can be determined either directly or indirectly as described above. In one such embodiment, the assay comprises
10 contacting the NOVX protein or biologically-active portion thereof with a known compound which binds NOVX to form an assay mixture, contacting the assay mixture with a test compound, and determining the ability of the test compound to interact with an NOVX protein, wherein determining the ability of the test compound to interact with an NOVX protein comprises determining the ability of the test compound to preferentially bind to NOVX
15 or biologically-active portion thereof as compared to the known compound.

 In still another embodiment, an assay is a cell-free assay comprising contacting NOVX protein or biologically-active portion thereof with a test compound and determining the ability of the test compound to modulate (*e.g.* stimulate or inhibit) the activity of the NOVX protein or biologically-active portion thereof. Determining the ability of the test compound to
20 modulate the activity of NOVX can be accomplished, for example, by determining the ability of the NOVX protein to bind to an NOVX target molecule by one of the methods described above for determining direct binding. In an alternative embodiment, determining the ability of the test compound to modulate the activity of NOVX protein can be accomplished by determining the ability of the NOVX protein further modulate an NOVX target molecule. For
25 example, the catalytic/enzymatic activity of the target molecule on an appropriate substrate can be determined as described, *supra*.

 In yet another embodiment, the cell-free assay comprises contacting the NOVX protein or biologically-active portion thereof with a known compound which binds NOVX protein to form an assay mixture, contacting the assay mixture with a test compound, and determining
30 the ability of the test compound to interact with an NOVX protein, wherein determining the ability of the test compound to interact with an NOVX protein comprises determining the ability of the NOVX protein to preferentially bind to or modulate the activity of an NOVX target molecule.

The cell-free assays of the invention are amenable to use of both the soluble form or the membrane-bound form of NOVX protein. In the case of cell-free assays comprising the membrane-bound form of NOVX protein, it may be desirable to utilize a solubilizing agent such that the membrane-bound form of NOVX protein is maintained in solution. Examples of
5 such solubilizing agents include non-ionic detergents such as n-octylglucoside, n-dodecylglucoside, n-dodecylmaltoside, octanoyl-N-methylglucamide, decanoyl-N-methylglucamide, Triton[®] X-100, Triton[®] X-114, Thesit[®], Isotridecypoly(ethylene glycol ether)_n, N-dodecyl--N,N-dimethyl-3-ammonio-1-propane sulfonate, 3-(3-cholamidopropyl) dimethylamminiol-1-propane sulfonate (CHAPS), or
10 3-(3-cholamidopropyl)dimethylamminiol-2-hydroxy-1-propane sulfonate (CHAPSO).

In more than one embodiment of the above assay methods of the invention, it may be desirable to immobilize either NOVX protein or its target molecule to facilitate separation of complexed from uncomplexed forms of one or both of the proteins, as well as to accommodate automation of the assay. Binding of a test compound to NOVX protein, or interaction of
15 NOVX protein with a target molecule in the presence and absence of a candidate compound, can be accomplished in any vessel suitable for containing the reactants. Examples of such vessels include microtiter plates, test tubes, and micro-centrifuge tubes. In one embodiment, a fusion protein can be provided that adds a domain that allows one or both of the proteins to be bound to a matrix. For example, GST-NOVX fusion proteins or GST-target fusion proteins
20 can be adsorbed onto glutathione sepharose beads (Sigma Chemical, St. Louis, MO) or glutathione derivatized microtiter plates, that are then combined with the test compound or the test compound and either the non-adsorbed target protein or NOVX protein, and the mixture is incubated under conditions conducive to complex formation (*e.g.*, at physiological conditions for salt and pH). Following incubation, the beads or microtiter plate wells are washed to
25 remove any unbound components, the matrix immobilized in the case of beads, complex determined either directly or indirectly, for example, as described, *supra*. Alternatively, the complexes can be dissociated from the matrix, and the level of NOVX protein binding or activity determined using standard techniques.

Other techniques for immobilizing proteins on matrices can also be used in the
30 screening assays of the invention. For example, either the NOVX protein or its target molecule can be immobilized utilizing conjugation of biotin and streptavidin. Biotinylated NOVX protein or target molecules can be prepared from biotin-NHS (N-hydroxy-succinimide) using techniques well-known within the art (*e.g.*, biotinylation kit, Pierce Chemicals, Rockford, Ill.), and immobilized in the wells of streptavidin-coated 96 well

plates (Pierce Chemical). Alternatively, antibodies reactive with NOVX protein or target molecules, but which do not interfere with binding of the NOVX protein to its target molecule, can be derivatized to the wells of the plate, and unbound target or NOVX protein trapped in the wells by antibody conjugation. Methods for detecting such complexes, in addition to those described above for the GST-immobilized complexes, include immunodetection of complexes using antibodies reactive with the NOVX protein or target molecule, as well as enzyme-linked assays that rely on detecting an enzymatic activity associated with the NOVX protein or target molecule.

In another embodiment, modulators of NOVX protein expression are identified in a method wherein a cell is contacted with a candidate compound and the expression of NOVX mRNA or protein in the cell is determined. The level of expression of NOVX mRNA or protein in the presence of the candidate compound is compared to the level of expression of NOVX mRNA or protein in the absence of the candidate compound. The candidate compound can then be identified as a modulator of NOVX mRNA or protein expression based upon this comparison. For example, when expression of NOVX mRNA or protein is greater (*i.e.*, statistically significantly greater) in the presence of the candidate compound than in its absence, the candidate compound is identified as a stimulator of NOVX mRNA or protein expression. Alternatively, when expression of NOVX mRNA or protein is less (statistically significantly less) in the presence of the candidate compound than in its absence, the candidate compound is identified as an inhibitor of NOVX mRNA or protein expression. The level of NOVX mRNA or protein expression in the cells can be determined by methods described herein for detecting NOVX mRNA or protein.

In yet another aspect of the invention, the NOVX proteins can be used as "bait proteins" in a two-hybrid assay or three hybrid assay (*see, e.g.*, U.S. Patent No. 5,283,317; Zervos, *et al.*, 1993. *Cell* 72: 223-232; Madura, *et al.*, 1993. *J. Biol. Chem.* 268: 12046-12054; Bartel, *et al.*, 1993. *Biotechniques* 14: 920-924; Iwabuchi, *et al.*, 1993. *Oncogene* 8: 1693-1696; and Brent WO 94/10300), to identify other proteins that bind to or interact with NOVX ("NOVX-binding proteins" or "NOVX-bp") and modulate NOVX activity. Such NOVX-binding proteins are also likely to be involved in the propagation of signals by the NOVX proteins as, for example, upstream or downstream elements of the NOVX pathway.

The two-hybrid system is based on the modular nature of most transcription factors, which consist of separable DNA-binding and activation domains. Briefly, the assay utilizes two different DNA constructs. In one construct, the gene that codes for NOVX is fused to a gene encoding the DNA binding domain of a known transcription factor (*e.g.*, GAL-4). In the

other construct, a DNA sequence, from a library of DNA sequences, that encodes an unidentified protein ("prey" or "sample") is fused to a gene that codes for the activation domain of the known transcription factor. If the "bait" and the "prey" proteins are able to interact, *in vivo*, forming an NOVX-dependent complex, the DNA-binding and activation domains of the transcription factor are brought into close proximity. This proximity allows transcription of a reporter gene (*e.g.*, LacZ) that is operably linked to a transcriptional regulatory site responsive to the transcription factor. Expression of the reporter gene can be detected and cell colonies containing the functional transcription factor can be isolated and used to obtain the cloned gene that encodes the protein which interacts with NOVX.

The invention further pertains to novel agents identified by the aforementioned screening assays and uses thereof for treatments as described herein.

Detection Assays

Portions or fragments of the cDNA sequences identified herein (and the corresponding complete gene sequences) can be used in numerous ways as polynucleotide reagents. By way of example, and not of limitation, these sequences can be used to: (i) map their respective genes on a chromosome; and, thus, locate gene regions associated with genetic disease; (ii) identify an individual from a minute biological sample (tissue typing); and (iii) aid in forensic identification of a biological sample. Some of these applications are described in the subsections, below.

Chromosome Mapping

Once the sequence (or a portion of the sequence) of a gene has been isolated, this sequence can be used to map the location of the gene on a chromosome. This process is called chromosome mapping. Accordingly, portions or fragments of the NOVX sequences, SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, and 217, or fragments or derivatives thereof, can be used to map the location of the NOVX genes, respectively, on a chromosome. The mapping of the NOVX sequences to chromosomes is an important first step in correlating these sequences with genes associated with disease.

Briefly, NOVX genes can be mapped to chromosomes by preparing PCR primers (preferably 15-25 bp in length) from the NOVX sequences. Computer analysis of the NOVX sequences can be used to rapidly select primers that do not span more than one exon in the genomic DNA, thus complicating the amplification process. These primers can then be used for PCR screening of somatic cell hybrids containing individual human chromosomes. Only

those hybrids containing the human gene corresponding to the NOVX sequences will yield an amplified fragment.

Somatic cell hybrids are prepared by fusing somatic cells from different mammals (e.g., human and mouse cells). As hybrids of human and mouse cells grow and divide, they gradually lose human chromosomes in random order, but retain the mouse chromosomes. By using media in which mouse cells cannot grow, because they lack a particular enzyme, but in which human cells can, the one human chromosome that contains the gene encoding the needed enzyme will be retained. By using various media, panels of hybrid cell lines can be established. Each cell line in a panel contains either a single human chromosome or a small number of human chromosomes, and a full set of mouse chromosomes, allowing easy mapping of individual genes to specific human chromosomes. See, e.g., D'Eustachio, *et al.*, 1983. *Science* 220: 919-924. Somatic cell hybrids containing only fragments of human chromosomes can also be produced by using human chromosomes with translocations and deletions.

PCR mapping of somatic cell hybrids is a rapid procedure for assigning a particular sequence to a particular chromosome. Three or more sequences can be assigned per day using a single thermal cycler. Using the NOVX sequences to design oligonucleotide primers, sub-localization can be achieved with panels of fragments from specific chromosomes.

Fluorescence *in situ* hybridization (FISH) of a DNA sequence to a metaphase chromosomal spread can further be used to provide a precise chromosomal location in one step. Chromosome spreads can be made using cells whose division has been blocked in metaphase by a chemical like colcemid that disrupts the mitotic spindle. The chromosomes can be treated briefly with trypsin, and then stained with Giemsa. A pattern of light and dark bands develops on each chromosome, so that the chromosomes can be identified individually. The FISH technique can be used with a DNA sequence as short as 500 or 600 bases. However, clones larger than 1,000 bases have a higher likelihood of binding to a unique chromosomal location with sufficient signal intensity for simple detection. Preferably 1,000 bases, and more preferably 2,000 bases, will suffice to get good results at a reasonable amount of time. For a review of this technique, see, Verma, *et al.*, HUMAN CHROMOSOMES: A MANUAL OF BASIC TECHNIQUES (Pergamon Press, New York 1988).

Reagents for chromosome mapping can be used individually to mark a single chromosome or a single site on that chromosome, or panels of reagents can be used for marking multiple sites and/or multiple chromosomes. Reagents corresponding to noncoding regions of the genes actually are preferred for mapping purposes. Coding sequences are more

likely to be conserved within gene families, thus increasing the chance of cross hybridizations during chromosomal mapping.

Once a sequence has been mapped to a precise chromosomal location, the physical position of the sequence on the chromosome can be correlated with genetic map data. Such data are found, *e.g.*, in McKusick, MENDELIAN INHERITANCE IN MAN, available on-line through Johns Hopkins University Welch Medical Library). The relationship between genes and disease, mapped to the same chromosomal region, can then be identified through linkage analysis (co-inheritance of physically adjacent genes), described in, *e.g.*, Egeland, *et al.*, 1987. *Nature*, 325: 783-787.

Moreover, differences in the DNA sequences between individuals affected and unaffected with a disease associated with the NOVX gene, can be determined. If a mutation is observed in some or all of the affected individuals but not in any unaffected individuals, then the mutation is likely to be the causative agent of the particular disease. Comparison of affected and unaffected individuals generally involves first looking for structural alterations in the chromosomes, such as deletions or translocations that are visible from chromosome spreads or detectable using PCR based on that DNA sequence. Ultimately, complete sequencing of genes from several individuals can be performed to confirm the presence of a mutation and to distinguish mutations from polymorphisms.

Tissue Typing

The NOVX sequences of the invention can also be used to identify individuals from minute biological samples. In this technique, an individual's genomic DNA is digested with one or more restriction enzymes, and probed on a Southern blot to yield unique bands for identification. The sequences of the invention are useful as additional DNA markers for RFLP ("restriction fragment length polymorphisms," described in U.S. Patent No. 5,272,057).

Furthermore, the sequences of the invention can be used to provide an alternative technique that determines the actual base-by-base DNA sequence of selected portions of an individual's genome. Thus, the NOVX sequences described herein can be used to prepare two PCR primers from the 5'- and 3'-termini of the sequences. These primers can then be used to amplify an individual's DNA and subsequently sequence it.

Panels of corresponding DNA sequences from individuals, prepared in this manner, can provide unique individual identifications, as each individual will have a unique set of such DNA sequences due to allelic differences. The sequences of the invention can be used to obtain such identification sequences from individuals and from tissue. The NOVX sequences

of the invention uniquely represent portions of the human genome. Allelic variation occurs to some degree in the coding regions of these sequences, and to a greater degree in the noncoding regions. It is estimated that allelic variation between individual humans occurs with a frequency of about once per each 500 bases. Much of the allelic variation is due to single nucleotide polymorphisms (SNPs), which include restriction fragment length polymorphisms (RFLPs).

Each of the sequences described herein can, to some degree, be used as a standard against which DNA from an individual can be compared for identification purposes. Because greater numbers of polymorphisms occur in the noncoding regions, fewer sequences are necessary to differentiate individuals. The noncoding sequences can comfortably provide positive individual identification with a panel of perhaps 10 to 1,000 primers that each yield a noncoding amplified sequence of 100 bases. If predicted coding sequences, such as those in SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, and 217 are used, a more appropriate number of primers for positive individual identification would be 500-2,000.

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Predictive Medicine

The invention also pertains to the field of predictive medicine in which diagnostic assays, prognostic assays, pharmacogenomics, and monitoring clinical trials are used for prognostic (predictive) purposes to thereby treat an individual prophylactically. Accordingly, one aspect of the invention relates to diagnostic assays for determining NOVX protein and/or nucleic acid expression as well as NOVX activity, in the context of a biological sample (*e.g.*, blood, serum, cells, tissue) to thereby determine whether an individual is afflicted with a disease or disorder, or is at risk of developing a disorder, associated with aberrant NOVX expression or activity. The disorders include metabolic disorders, diabetes, obesity, infectious disease, anorexia, cancer-associated cachexia, cancer, neurodegenerative disorders, Alzheimer's Disease, Parkinson's Disorder, immune disorders, and hematopoietic disorders, and the various dyslipidemias, metabolic disturbances associated with obesity, the metabolic syndrome X and wasting disorders associated with chronic diseases and various cancers. The invention also provides for prognostic (or predictive) assays for determining whether an individual is at risk of developing a disorder associated with NOVX protein, nucleic acid expression or activity. For example, mutations in an NOVX gene can be assayed in a biological sample. Such assays can be used for prognostic or predictive purpose to thereby prophylactically treat an individual prior to the onset of a disorder characterized by or associated with NOVX protein, nucleic acid expression, or biological activity.

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Another aspect of the invention provides methods for determining NOVX protein, nucleic acid expression or activity in an individual to thereby select appropriate therapeutic or prophylactic agents for that individual (referred to herein as "pharmacogenomics").

Pharmacogenomics allows for the selection of agents (*e.g.*, drugs) for therapeutic or prophylactic treatment of an individual based on the genotype of the individual (*e.g.*, the genotype of the individual examined to determine the ability of the individual to respond to a particular agent.)

Yet another aspect of the invention pertains to monitoring the influence of agents (*e.g.*, drugs, compounds) on the expression or activity of NOVX in clinical trials.

These and other agents are described in further detail in the following sections.

Diagnostic Assays

An exemplary method for detecting the presence or absence of NOVX in a biological sample involves obtaining a biological sample from a test subject and contacting the biological sample with a compound or an agent capable of detecting NOVX protein or nucleic acid (*e.g.*, mRNA, genomic DNA) that encodes NOVX protein such that the presence of NOVX is detected in the biological sample. An agent for detecting NOVX mRNA or genomic DNA is a labeled nucleic acid probe capable of hybridizing to NOVX mRNA or genomic DNA. The nucleic acid probe can be, for example, a full-length NOVX nucleic acid, such as the nucleic acid of SEQ ID NOS:1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, and 217, or a portion thereof, such as an oligonucleotide of at least 15, 30, 50, 100, 250 or 500 nucleotides in length and sufficient to specifically hybridize under stringent conditions to NOVX mRNA or genomic DNA. Other suitable probes for use in the diagnostic assays of the invention are described herein.

An agent for detecting NOVX protein is an antibody capable of binding to NOVX protein, preferably an antibody with a detectable label. Antibodies can be polyclonal, or more preferably, monoclonal. An intact antibody, or a fragment thereof (*e.g.*, Fab or F(ab')₂) can be used. The term "labeled", with regard to the probe or antibody, is intended to encompass direct labeling of the probe or antibody by coupling (*i.e.*, physically linking) a detectable substance to the probe or antibody, as well as indirect labeling of the probe or antibody by reactivity with another reagent that is directly labeled. Examples of indirect labeling include detection of a primary antibody using a fluorescently-labeled secondary antibody and end-labeling of a DNA probe with biotin such that it can be detected with fluorescently-labeled streptavidin. The term "biological sample" is intended to include tissues, cells and

biological fluids isolated from a subject, as well as tissues, cells and fluids present within a subject. That is, the detection method of the invention can be used to detect NOVX mRNA, protein, or genomic DNA in a biological sample *in vitro* as well as *in vivo*. For example, *in vitro* techniques for detection of NOVX mRNA include Northern hybridizations and *in situ* hybridizations. *In vitro* techniques for detection of NOVX protein include enzyme linked immunosorbent assays (ELISAs), Western blots, immunoprecipitations, and immunofluorescence. *In vitro* techniques for detection of NOVX genomic DNA include Southern hybridizations. Furthermore, *in vivo* techniques for detection of NOVX protein include introducing into a subject a labeled anti-NOVX antibody. For example, the antibody can be labeled with a radioactive marker whose presence and location in a subject can be detected by standard imaging techniques.

In one embodiment, the biological sample contains protein molecules from the test subject. Alternatively, the biological sample can contain mRNA molecules from the test subject or genomic DNA molecules from the test subject. A preferred biological sample is a peripheral blood leukocyte sample isolated by conventional means from a subject.

In another embodiment, the methods further involve obtaining a control biological sample from a control subject, contacting the control sample with a compound or agent capable of detecting NOVX protein, mRNA, or genomic DNA, such that the presence of NOVX protein, mRNA or genomic DNA is detected in the biological sample, and comparing the presence of NOVX protein, mRNA or genomic DNA in the control sample with the presence of NOVX protein, mRNA or genomic DNA in the test sample.

The invention also encompasses kits for detecting the presence of NOVX in a biological sample. For example, the kit can comprise: a labeled compound or agent capable of detecting NOVX protein or mRNA in a biological sample; means for determining the amount of NOVX in the sample; and means for comparing the amount of NOVX in the sample with a standard. The compound or agent can be packaged in a suitable container. The kit can further comprise instructions for using the kit to detect NOVX protein or nucleic acid.

Prognostic Assays

The diagnostic methods described herein can furthermore be utilized to identify subjects having or at risk of developing a disease or disorder associated with aberrant NOVX expression or activity. For example, the assays described herein, such as the preceding diagnostic assays or the following assays, can be utilized to identify a subject having or at risk of developing a disorder associated with NOVX protein, nucleic acid expression or activity.

Alternatively, the prognostic assays can be utilized to identify a subject having or at risk for developing a disease or disorder. Thus, the invention provides a method for identifying a disease or disorder associated with aberrant NOVX expression or activity in which a test sample is obtained from a subject and NOVX protein or nucleic acid (*e.g.*, mRNA, genomic DNA) is detected, wherein the presence of NOVX protein or nucleic acid is diagnostic for a subject having or at risk of developing a disease or disorder associated with aberrant NOVX expression or activity. As used herein, a "test sample" refers to a biological sample obtained from a subject of interest. For example, a test sample can be a biological fluid (*e.g.*, serum), cell sample, or tissue.

Furthermore, the prognostic assays described herein can be used to determine whether a subject can be administered an agent (*e.g.*, an agonist, antagonist, peptidomimetic, protein, peptide, nucleic acid, small molecule, or other drug candidate) to treat a disease or disorder associated with aberrant NOVX expression or activity. For example, such methods can be used to determine whether a subject can be effectively treated with an agent for a disorder. Thus, the invention provides methods for determining whether a subject can be effectively treated with an agent for a disorder associated with aberrant NOVX expression or activity in which a test sample is obtained and NOVX protein or nucleic acid is detected (*e.g.*, wherein the presence of NOVX protein or nucleic acid is diagnostic for a subject that can be administered the agent to treat a disorder associated with aberrant NOVX expression or activity).

The methods of the invention can also be used to detect genetic lesions in an NOVX gene, thereby determining if a subject with the lesioned gene is at risk for a disorder characterized by aberrant cell proliferation and/or differentiation. In various embodiments, the methods include detecting, in a sample of cells from the subject, the presence or absence of a genetic lesion characterized by at least one of an alteration affecting the integrity of a gene encoding an NOVX-protein, or the misexpression of the NOVX gene. For example, such genetic lesions can be detected by ascertaining the existence of at least one of: (i) a deletion of one or more nucleotides from an NOVX gene; (ii) an addition of one or more nucleotides to an NOVX gene; (iii) a substitution of one or more nucleotides of an NOVX gene, (iv) a chromosomal rearrangement of an NOVX gene; (v) an alteration in the level of a messenger RNA transcript of an NOVX gene, (vi) aberrant modification of an NOVX gene, such as of the methylation pattern of the genomic DNA, (vii) the presence of a non-wild-type splicing pattern of a messenger RNA transcript of an NOVX gene, (viii) a non-wild-type level of an NOVX protein, (ix) allelic loss of an NOVX gene, and (x) inappropriate post-translational

modification of an NOVX protein. As described herein, there are a large number of assay techniques known in the art which can be used for detecting lesions in an NOVX gene. A preferred biological sample is a peripheral blood leukocyte sample isolated by conventional means from a subject. However, any biological sample containing nucleated cells may be
5 used, including, for example, buccal mucosal cells.

In certain embodiments, detection of the lesion involves the use of a probe/primer in a polymerase chain reaction (PCR) (*see, e.g.,* U.S. Patent Nos. 4,683,195 and 4,683,202), such as anchor PCR or RACE PCR, or, alternatively, in a ligation chain reaction (LCR) (*see, e.g.,* Landegran, *et al.*, 1988. *Science* 241: 1077-1080; and Nakazawa, *et al.*, 1994. *Proc. Natl.*
10 *Acad. Sci. USA* 91: 360-364), the latter of which can be particularly useful for detecting point mutations in the NOVX-gene (*see, Abravaya, et al.*, 1995. *Nucl. Acids Res.* 23: 675-682). This method can include the steps of collecting a sample of cells from a patient, isolating nucleic acid (*e.g.,* genomic, mRNA or both) from the cells of the sample, contacting the nucleic acid sample with one or more primers that specifically hybridize to an NOVX gene
15 under conditions such that hybridization and amplification of the NOVX gene (if present) occurs, and detecting the presence or absence of an amplification product, or detecting the size of the amplification product and comparing the length to a control sample. It is anticipated that PCR and/or LCR may be desirable to use as a preliminary amplification step in conjunction with any of the techniques used for detecting mutations described herein.

Alternative amplification methods include: self sustained sequence replication (*see, Guatelli, et al.*, 1990. *Proc. Natl. Acad. Sci. USA* 87: 1874-1878), transcriptional amplification system (*see, Kwoh, et al.*, 1989. *Proc. Natl. Acad. Sci. USA* 86: 1173-1177); Q β Replicase (*see, Lizardi, et al.*, 1988. *BioTechnology* 6: 1197), or any other nucleic acid amplification method, followed by the detection of the amplified molecules using techniques well known to
25 those of skill in the art. These detection schemes are especially useful for the detection of nucleic acid molecules if such molecules are present in very low numbers.

In an alternative embodiment, mutations in an NOVX gene from a sample cell can be identified by alterations in restriction enzyme cleavage patterns. For example, sample and control DNA is isolated, amplified (optionally), digested with one or more restriction
30 endonucleases, and fragment length sizes are determined by gel electrophoresis and compared. Differences in fragment length sizes between sample and control DNA indicates mutations in the sample DNA. Moreover, the use of sequence specific ribozymes (*see, e.g.,* U.S. Patent No. 5,493,531) can be used to score for the presence of specific mutations by development or loss of a ribozyme cleavage site.

In other embodiments, genetic mutations in NOVX can be identified by hybridizing a sample and control nucleic acids, *e.g.*, DNA or RNA, to high-density arrays containing hundreds or thousands of oligonucleotides probes. *See, e.g.*, Cronin, *et al.*, 1996. *Human Mutation* 7: 244-255; Kozal, *et al.*, 1996. *Nat. Med.* 2: 753-759. For example, genetic mutations in NOVX can be identified in two dimensional arrays containing light-generated DNA probes as described in Cronin, *et al.*, *supra*. Briefly, a first hybridization array of probes can be used to scan through long stretches of DNA in a sample and control to identify base changes between the sequences by making linear arrays of sequential overlapping probes. This step allows the identification of point mutations. This is followed by a second hybridization array that allows the characterization of specific mutations by using smaller, specialized probe arrays complementary to all variants or mutations detected. Each mutation array is composed of parallel probe sets, one complementary to the wild-type gene and the other complementary to the mutant gene.

In yet another embodiment, any of a variety of sequencing reactions known in the art can be used to directly sequence the NOVX gene and detect mutations by comparing the sequence of the sample NOVX with the corresponding wild-type (control) sequence. Examples of sequencing reactions include those based on techniques developed by Maxim and Gilbert, 1977. *Proc. Natl. Acad. Sci. USA* 74: 560 or Sanger, 1977. *Proc. Natl. Acad. Sci. USA* 74: 5463. It is also contemplated that any of a variety of automated sequencing procedures can be utilized when performing the diagnostic assays (*see, e.g.*, Naeve, *et al.*, 1995. *Biotechniques* 19: 448), including sequencing by mass spectrometry (*see, e.g.*, PCT International Publication No. WO 94/16101; Cohen, *et al.*, 1996. *Adv. Chromatography* 36: 127-162; and Griffin, *et al.*, 1993. *Appl. Biochem. Biotechnol.* 38: 147-159).

Other methods for detecting mutations in the NOVX gene include methods in which protection from cleavage agents is used to detect mismatched bases in RNA/RNA or RNA/DNA heteroduplexes. *See, e.g.*, Myers, *et al.*, 1985. *Science* 230: 1242. In general, the art technique of "mismatch cleavage" starts by providing heteroduplexes of formed by hybridizing (labeled) RNA or DNA containing the wild-type NOVX sequence with potentially mutant RNA or DNA obtained from a tissue sample. The double-stranded duplexes are treated with an agent that cleaves single-stranded regions of the duplex such as which will exist due to basepair mismatches between the control and sample strands. For instance, RNA/DNA duplexes can be treated with RNase and DNA/DNA hybrids treated with S₁ nuclease to enzymatically digesting the mismatched regions. In other embodiments, either DNA/DNA or RNA/DNA duplexes can be treated with hydroxylamine or osmium tetroxide

and with piperidine in order to digest mismatched regions. After digestion of the mismatched regions, the resulting material is then separated by size on denaturing polyacrylamide gels to determine the site of mutation. *See, e.g., Cotton, et al., 1988. Proc. Natl. Acad. Sci. USA 85: 4397; Saleeba, et al., 1992. Methods Enzymol. 217: 286-295.* In an embodiment, the control
5 DNA or RNA can be labeled for detection.

In still another embodiment, the mismatch cleavage reaction employs one or more proteins that recognize mismatched base pairs in double-stranded DNA (so called "DNA mismatch repair" enzymes) in defined systems for detecting and mapping point mutations in NOVX cDNAs obtained from samples of cells. For example, the mutY enzyme of *E. coli*
10 cleaves A at G/A mismatches and the thymidine DNA glycosylase from HeLa cells cleaves T at G/T mismatches. *See, e.g., Hsu, et al., 1994. Carcinogenesis 15: 1657-1662.* According to an exemplary embodiment, a probe based on an NOVX sequence, *e.g., a wild-type NOVX* sequence, is hybridized to a cDNA or other DNA product from a test cell(s). The duplex is treated with a DNA mismatch repair enzyme, and the cleavage products, if any, can be
15 detected from electrophoresis protocols or the like. *See, e.g., U.S. Patent No. 5,459,039.*

In other embodiments, alterations in electrophoretic mobility will be used to identify mutations in NOVX genes. For example, single strand conformation polymorphism (SSCP) may be used to detect differences in electrophoretic mobility between mutant and wild type nucleic acids. *See, e.g., Orita, et al., 1989. Proc. Natl. Acad. Sci. USA: 86: 2766; Cotton,*
20 *1993. Mutat. Res. 285: 125-144; Hayashi, 1992. Genet. Anal. Tech. Appl. 9: 73-79.* Single-stranded DNA fragments of sample and control NOVX nucleic acids will be denatured and allowed to renature. The secondary structure of single-stranded nucleic acids varies according to sequence, the resulting alteration in electrophoretic mobility enables the detection of even a single base change. The DNA fragments may be labeled or detected with labeled
25 probes. The sensitivity of the assay may be enhanced by using RNA (rather than DNA), in which the secondary structure is more sensitive to a change in sequence. In one embodiment, the subject method utilizes heteroduplex analysis to separate double stranded heteroduplex molecules on the basis of changes in electrophoretic mobility. *See, e.g., Keen, et al., 1991. Trends Genet. 7: 5.*

In yet another embodiment, the movement of mutant or wild-type fragments in polyacrylamide gels containing a gradient of denaturant is assayed using denaturing gradient gel electrophoresis (DGGE). *See, e.g., Myers, et al., 1985. Nature 313: 495.* When DGGE is used as the method of analysis, DNA will be modified to insure that it does not completely denature, for example by adding a GC clamp of approximately 40 bp of high-melting GC-rich

DNA by PCR. In a further embodiment, a temperature gradient is used in place of a denaturing gradient to identify differences in the mobility of control and sample DNA. *See, e.g., Rosenbaum and Reissner, 1987. Biophys. Chem. 265: 12753.*

5 Examples of other techniques for detecting point mutations include, but are not limited to, selective oligonucleotide hybridization, selective amplification, or selective primer extension. For example, oligonucleotide primers may be prepared in which the known mutation is placed centrally and then hybridized to target DNA under conditions that permit hybridization only if a perfect match is found. *See, e.g., Saiki, et al., 1986. Nature 324: 163; Saiki, et al., 1989. Proc. Natl. Acad. Sci. USA 86: 6230.* Such allele specific oligonucleotides
10 are hybridized to PCR amplified target DNA or a number of different mutations when the oligonucleotides are attached to the hybridizing membrane and hybridized with labeled target DNA.

Alternatively, allele specific amplification technology that depends on selective PCR amplification may be used in conjunction with the instant invention. Oligonucleotides used as
15 primers for specific amplification may carry the mutation of interest in the center of the molecule (so that amplification depends on differential hybridization; *see, e.g., Gibbs, et al., 1989. Nucl. Acids Res. 17: 2437-2448*) or at the extreme 3'-terminus of one primer where, under appropriate conditions, mismatch can prevent, or reduce polymerase extension (*see, e.g., Prossner, 1993. Tibtech. 11: 238*). In addition it may be desirable to introduce a novel
20 restriction site in the region of the mutation to create cleavage-based detection. *See, e.g., Gasparini, et al., 1992. Mol. Cell Probes 6: 1.* It is anticipated that in certain embodiments amplification may also be performed using *Taq* ligase for amplification. *See, e.g., Barany, 1991. Proc. Natl. Acad. Sci. USA 88: 189.* In such cases, ligation will occur only if there is a perfect match at the 3'-terminus of the 5' sequence, making it possible to detect the presence of
25 a known mutation at a specific site by looking for the presence or absence of amplification.

The methods described herein may be performed, for example, by utilizing pre-packaged diagnostic kits comprising at least one probe nucleic acid or antibody reagent described herein, which may be conveniently used, *e.g.,* in clinical settings to diagnose
30 patients exhibiting symptoms or family history of a disease or illness involving an NOVX gene.

Furthermore, any cell type or tissue, preferably peripheral blood leukocytes, in which NOVX is expressed may be utilized in the prognostic assays described herein. However, any biological sample containing nucleated cells may be used, including, for example, buccal mucosal cells.

Pharmacogenomics

Agents, or modulators that have a stimulatory or inhibitory effect on NOVX activity (e.g., NOVX gene expression), as identified by a screening assay described herein can be administered to individuals to treat (prophylactically or therapeutically) disorders (The disorders include metabolic disorders, diabetes, obesity, infectious disease, anorexia, cancer-associated cachexia, cancer, neurodegenerative disorders, Alzheimer's Disease, Parkinson's Disorder, immune disorders, and hematopoietic disorders, and the various dyslipidemias, metabolic disturbances associated with obesity, the metabolic syndrome X and wasting disorders associated with chronic diseases and various cancers.) In conjunction with such treatment, the pharmacogenomics (i.e., the study of the relationship between an individual's genotype and that individual's response to a foreign compound or drug) of the individual may be considered. Differences in metabolism of therapeutics can lead to severe toxicity or therapeutic failure by altering the relation between dose and blood concentration of the pharmacologically active drug. Thus, the pharmacogenomics of the individual permits the selection of effective agents (e.g., drugs) for prophylactic or therapeutic treatments based on a consideration of the individual's genotype. Such pharmacogenomics can further be used to determine appropriate dosages and therapeutic regimens. Accordingly, the activity of NOVX protein, expression of NOVX nucleic acid, or mutation content of NOVX genes in an individual can be determined to thereby select appropriate agent(s) for therapeutic or prophylactic treatment of the individual.

Pharmacogenomics deals with clinically significant hereditary variations in the response to drugs due to altered drug disposition and abnormal action in affected persons. See e.g., Eichelbaum, 1996. *Clin. Exp. Pharmacol. Physiol.*, 23: 983-985; Linder, 1997. *Clin. Chem.*, 43: 254-266. In general, two types of pharmacogenetic conditions can be differentiated. Genetic conditions transmitted as a single factor altering the way drugs act on the body (altered drug action) or genetic conditions transmitted as single factors altering the way the body acts on drugs (altered drug metabolism). These pharmacogenetic conditions can occur either as rare defects or as polymorphisms. For example, glucose-6-phosphate dehydrogenase (G6PD) deficiency is a common inherited enzymopathy in which the main clinical complication is hemolysis after ingestion of oxidant drugs (anti-malarials, sulfonamides, analgesics, nitrofurans) and consumption of fava beans.

As an illustrative embodiment, the activity of drug metabolizing enzymes is a major determinant of both the intensity and duration of drug action. The discovery of genetic

polymorphisms of drug metabolizing enzymes (*e.g.*, N-acetyltransferase 2 (NAT 2) and cytochrome P450 enzymes CYP2D6 and CYP2C19) has provided an explanation as to why some patients do not obtain the expected drug effects or show exaggerated drug response and serious toxicity after taking the standard and safe dose of a drug. These polymorphisms are expressed in two phenotypes in the population, the extensive metabolizer (EM) and poor metabolizer (PM). The prevalence of PM is different among different populations. For example, the gene coding for CYP2D6 is highly polymorphic and several mutations have been identified in PM, which all lead to the absence of functional CYP2D6. Poor metabolizers of CYP2D6 and CYP2C19 quite frequently experience exaggerated drug response and side effects when they receive standard doses. If a metabolite is the active therapeutic moiety, PM show no therapeutic response, as demonstrated for the analgesic effect of codeine mediated by its CYP2D6-formed metabolite morphine. At the other extreme are the so called ultra-rapid metabolizers who do not respond to standard doses. Recently, the molecular basis of ultra-rapid metabolism has been identified to be due to CYP2D6 gene amplification.

Thus, the activity of NOVX protein, expression of NOVX nucleic acid, or mutation content of NOVX genes in an individual can be determined to thereby select appropriate agent(s) for therapeutic or prophylactic treatment of the individual. In addition, pharmacogenetic studies can be used to apply genotyping of polymorphic alleles encoding drug-metabolizing enzymes to the identification of an individual's drug responsiveness phenotype. This knowledge, when applied to dosing or drug selection, can avoid adverse reactions or therapeutic failure and thus enhance therapeutic or prophylactic efficiency when treating a subject with an NOVX modulator, such as a modulator identified by one of the exemplary screening assays described herein.

Monitoring of Effects During Clinical Trials

Monitoring the influence of agents (*e.g.*, drugs, compounds) on the expression or activity of NOVX (*e.g.*, the ability to modulate aberrant cell proliferation and/or differentiation) can be applied not only in basic drug screening, but also in clinical trials. For example, the effectiveness of an agent determined by a screening assay as described herein to increase NOVX gene expression, protein levels, or upregulate NOVX activity, can be monitored in clinical trails of subjects exhibiting decreased NOVX gene expression, protein levels, or downregulated NOVX activity. Alternatively, the effectiveness of an agent determined by a screening assay to decrease NOVX gene expression, protein levels, or downregulate NOVX activity, can be monitored in clinical trails of subjects exhibiting

increased NOVX gene expression, protein levels, or upregulated NOVX activity. In such clinical trials, the expression or activity of NOVX and, preferably, other genes that have been implicated in, for example, a cellular proliferation or immune disorder can be used as a "read out" or markers of the immune responsiveness of a particular cell.

5 By way of example, and not of limitation, genes, including NOVX, that are modulated in cells by treatment with an agent (*e.g.*, compound, drug or small molecule) that modulates NOVX activity (*e.g.*, identified in a screening assay as described herein) can be identified. Thus, to study the effect of agents on cellular proliferation disorders, for example, in a clinical trial, cells can be isolated and RNA prepared and analyzed for the levels of expression of
10 NOVX and other genes implicated in the disorder. The levels of gene expression (*i.e.*, a gene expression pattern) can be quantified by Northern blot analysis or RT-PCR, as described herein, or alternatively by measuring the amount of protein produced, by one of the methods as described herein, or by measuring the levels of activity of NOVX or other genes. In this manner, the gene expression pattern can serve as a marker, indicative of the physiological
15 response of the cells to the agent. Accordingly, this response state may be determined before, and at various points during, treatment of the individual with the agent.

In one embodiment, the invention provides a method for monitoring the effectiveness of treatment of a subject with an agent (*e.g.*, an agonist, antagonist, protein, peptide, peptidomimetic, nucleic acid, small molecule, or other drug candidate identified by the
20 screening assays described herein) comprising the steps of (i) obtaining a pre-administration sample from a subject prior to administration of the agent; (ii) detecting the level of expression of an NOVX protein, mRNA, or genomic DNA in the preadministration sample; (iii) obtaining one or more post-administration samples from the subject; (iv) detecting the level of expression or activity of the NOVX protein, mRNA, or genomic DNA in the
25 post-administration samples; (v) comparing the level of expression or activity of the NOVX protein, mRNA, or genomic DNA in the pre-administration sample with the NOVX protein, mRNA, or genomic DNA in the post administration sample or samples; and (vi) altering the administration of the agent to the subject accordingly. For example, increased administration of the agent may be desirable to increase the expression or activity of NOVX to higher levels
30 than detected, *i.e.*, to increase the effectiveness of the agent. Alternatively, decreased administration of the agent may be desirable to decrease expression or activity of NOVX to lower levels than detected, *i.e.*, to decrease the effectiveness of the agent.

Methods of Treatment

The invention provides for both prophylactic and therapeutic methods of treating a subject at risk of (or susceptible to) a disorder or having a disorder associated with aberrant NOVX expression or activity. The disorders include cardiomyopathy, atherosclerosis, hypertension, congenital heart defects, aortic stenosis, atrial septal defect (ASD), atrioventricular (A-V) canal defect, ductus arteriosus, pulmonary stenosis, subaortic stenosis, ventricular septal defect (VSD), valve diseases, tuberous sclerosis, scleroderma, obesity, transplantation, adrenoleukodystrophy, congenital adrenal hyperplasia, prostate cancer, neoplasm; adenocarcinoma, lymphoma, uterus cancer, fertility, hemophilia, hypercoagulation, idiopathic thrombocytopenic purpura, immunodeficiencies, graft versus host disease, AIDS, bronchial asthma, Crohn's disease; multiple sclerosis, treatment of Albright Hereditary Osteodystrophy, and other diseases, disorders and conditions of the like.

These methods of treatment will be discussed more fully, below.

Disease and Disorders

Diseases and disorders that are characterized by increased (relative to a subject not suffering from the disease or disorder) levels or biological activity may be treated with Therapeutics that antagonize (*i.e.*, reduce or inhibit) activity. Therapeutics that antagonize activity may be administered in a therapeutic or prophylactic manner. Therapeutics that may be utilized include, but are not limited to: (i) an aforementioned peptide, or analogs, derivatives, fragments or homologs thereof; (ii) antibodies to an aforementioned peptide; (iii) nucleic acids encoding an aforementioned peptide; (iv) administration of antisense nucleic acid and nucleic acids that are "dysfunctional" (*i.e.*, due to a heterologous insertion within the coding sequences of coding sequences to an aforementioned peptide) that are utilized to "knockout" endogenous function of an aforementioned peptide by homologous recombination (*see, e.g.*, Capecchi, 1989. *Science* 244: 1288-1292); or (v) modulators (*i.e.*, inhibitors, agonists and antagonists, including additional peptide mimetic of the invention or antibodies specific to a peptide of the invention) that alter the interaction between an aforementioned peptide and its binding partner.

Diseases and disorders that are characterized by decreased (relative to a subject not suffering from the disease or disorder) levels or biological activity may be treated with Therapeutics that increase (*i.e.*, are agonists to) activity. Therapeutics that upregulate activity may be administered in a therapeutic or prophylactic manner. Therapeutics that may be

Increased or decreased levels can be readily detected by quantifying peptide and/or RNA, by obtaining a patient tissue sample (*e.g.*, from biopsy tissue) and assaying it *in vitro* for RNA or peptide levels, structure and/or activity of the expressed peptides (or mRNAs of an aforementioned peptide). Methods that are well-known within the art include, but are not limited to, immunoassays (*e.g.*, by Western blot analysis, immunoprecipitation followed by sodium dodecyl sulfate (SDS) polyacrylamide gel electrophoresis, immunocytochemistry, etc.) and/or hybridization assays to detect expression of mRNAs (*e.g.*, Northern assays, dot blots, *in situ* hybridization, and the like).

Prophylactic Methods

In one aspect, the invention provides a method for preventing, in a subject, a disease or condition associated with an aberrant NOVX expression or activity, by administering to the subject an agent that modulates NOVX expression or at least one NOVX activity. Subjects at risk for a disease that is caused or contributed to by aberrant NOVX expression or activity can be identified by, for example, any or a combination of diagnostic or prognostic assays as described herein. Administration of a prophylactic agent can occur prior to the manifestation of symptoms characteristic of the NOVX aberrancy, such that a disease or disorder is prevented or, alternatively, delayed in its progression. Depending upon the type of NOVX aberrancy, for example, an NOVX agonist or NOVX antagonist agent can be used for treating the subject. The appropriate agent can be determined based on screening assays described herein. The prophylactic methods of the invention are further discussed in the following subsections.

Therapeutic Methods

Another aspect of the invention pertains to methods of modulating NOVX expression or activity for therapeutic purposes. The modulatory method of the invention involves contacting a cell with an agent that modulates one or more of the activities of NOVX protein activity associated with the cell. An agent that modulates NOVX protein activity can be an agent as described herein, such as a nucleic acid or a protein, a naturally-occurring cognate ligand of an NOVX protein, a peptide, an NOVX peptidomimetic, or other small molecule. In one embodiment, the agent stimulates one or more NOVX protein activity. Examples of such stimulatory agents include active NOVX protein and a nucleic acid molecule encoding NOVX

that has been introduced into the cell. In another embodiment, the agent inhibits one or more NOVX protein activity. Examples of such inhibitory agents include antisense NOVX nucleic acid molecules and anti-NOVX antibodies. These modulatory methods can be performed *in vitro* (e.g., by culturing the cell with the agent) or, alternatively, *in vivo* (e.g., by administering the agent to a subject). As such, the invention provides methods of treating an individual afflicted with a disease or disorder characterized by aberrant expression or activity of an NOVX protein or nucleic acid molecule. In one embodiment, the method involves administering an agent (e.g., an agent identified by a screening assay described herein), or combination of agents that modulates (e.g., up-regulates or down-regulates) NOVX expression or activity. In another embodiment, the method involves administering an NOVX protein or nucleic acid molecule as therapy to compensate for reduced or aberrant NOVX expression or activity.

Stimulation of NOVX activity is desirable *in situations* in which NOVX is abnormally downregulated and/or in which increased NOVX activity is likely to have a beneficial effect. One example of such a situation is where a subject has a disorder characterized by aberrant cell proliferation and/or differentiation (e.g., cancer or immune associated disorders). Another example of such a situation is where the subject has a gestational disease (e.g., preeclampsia).

Determination of the Biological Effect of the Therapeutic

In various embodiments of the invention, suitable *in vitro* or *in vivo* assays are performed to determine the effect of a specific Therapeutic and whether its administration is indicated for treatment of the affected tissue.

In various specific embodiments, *in vitro* assays may be performed with representative cells of the type(s) involved in the patient's disorder, to determine if a given Therapeutic exerts the desired effect upon the cell type(s). Compounds for use in therapy may be tested in suitable animal model systems including, but not limited to rats, mice, chicken, cows, monkeys, rabbits, and the like, prior to testing in human subjects. Similarly, for *in vivo* testing, any of the animal model system known in the art may be used prior to administration to human subjects.

Prophylactic and Therapeutic Uses of the Compositions of the Invention

The NOVX nucleic acids and proteins of the invention are useful in potential prophylactic and therapeutic applications implicated in a variety of disorders including, but not limited to: metabolic disorders, diabetes, obesity, infectious disease, anorexia, cancer-associated cancer, neurodegenerative disorders, Alzheimer's Disease, Parkinson's Disorder,

immune disorders, hematopoietic disorders, and the various dyslipidemias, metabolic disturbances associated with obesity, the metabolic syndrome X and wasting disorders associated with chronic diseases and various cancers.

As an example, a cDNA encoding the NOVX protein of the invention may be useful in gene therapy, and the protein may be useful when administered to a subject in need thereof. By way of non-limiting example, the compositions of the invention will have efficacy for treatment of patients suffering from: metabolic disorders, diabetes, obesity, infectious disease, anorexia, cancer-associated cachexia, cancer, neurodegenerative disorders, Alzheimer's Disease, Parkinson's Disorder, immune disorders, hematopoietic disorders, and the various dyslipidemias.

Both the novel nucleic acid encoding the NOVX protein, and the NOVX protein of the invention, or fragments thereof, may also be useful in diagnostic applications, wherein the presence or amount of the nucleic acid or the protein are to be assessed. A further use could be as an anti-bacterial molecule (*i.e.*, some peptides have been found to possess anti-bacterial properties). These materials are further useful in the generation of antibodies, which immunospecifically-bind to the novel substances of the invention for use in therapeutic or diagnostic methods.

The invention will be further described in the following examples, which do not limit the scope of the invention described in the claims.

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Examples

Example 1. Identification of NOVX clones

The novel NOVX target sequences identified in the present invention were subjected to the exon linking process to confirm the sequence. PCR primers were designed by starting at the most upstream sequence available, for the forward primer, and at the most downstream sequence available for the reverse primer. Table 13A shows the sequences of the PCR primers used for obtaining different clones. In each case, the sequence was examined, walking inward from the respective termini toward the coding sequence, until a suitable sequence that is either unique or highly selective was encountered, or, in the case of the reverse primer, until the stop codon was reached. Such primers were designed based on in silico predictions for the full length cDNA, part (one or more exons) of the DNA or protein sequence of the target sequence, or by translated homology of the predicted exons to closely related human sequences from other species. These primers were then employed in PCR amplification based

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on the following pool of human cDNAs: adrenal gland, bone marrow, brain - amygdala, brain - cerebellum, brain - hippocampus, brain - substantia nigra, brain - thalamus, brain -whole, fetal brain, fetal kidney, fetal liver, fetal lung, heart, kidney, lymphoma - Raji, mammary gland, pancreas, pituitary gland, placenta, prostate, salivary gland, skeletal muscle, small intestine, spinal cord, spleen, stomach, testis, thyroid, trachea, uterus. Usually the resulting amplicons were gel purified, cloned and sequenced to high redundancy. The PCR product derived from exon linking was cloned into the pCR2.1 vector from Invitrogen. The resulting bacterial clone has an insert covering the entire open reading frame cloned into the pCR2.1 vector. Table 13B shows a list of these bacterial clones. The resulting sequences from all clones were assembled with themselves, with other fragments in CuraGen Corporation's database and with public ESTs. Fragments and ESTs were included as components for an assembly when the extent of their identity with another component of the assembly was at least 95% over 50 bp. In addition, sequence traces were evaluated manually and edited for corrections if appropriate. These procedures provide the sequence reported herein.

Table 13A. PCR Primers for Exon Linking

NOVX Clone	Primer 1 (5' - 3')	SEQ ID NO	Primer 2 (5' - 3')	SEQ ID NO
NOV1a	AGACTGGGGCCAGGGAGACAG	119	CAGAGGCCAAACATCCCCATCAG	120
NOV1c	GAGACAGCCCTGGGGGAGA	121	ACCTGCCTCCTGCCAGTCC	122
NOV6	CATGTCCTCGACCGAGAGCGC	123	AGGTGGGGGGCTGCTTACTGCTT	124
NOV9a	GTCATGAAGGGGTTGCTG	125	GGTCAGCCCAGCCCCTCTG	126
NOV10	CGGCTGCTGGCATGGGTG	127	CTCCTGCTCTGTTTCCCCCTTCAT	128
NOV11a	GCCATGGTGCTGCTGCTGCT	129	GGCTCAGTCGGGGTAGATGATAAAGC	130
NOV11b	CGGGCGCGCCGTCGGAGT	131	CGGGCCGGCTCAGTCGGGGTAGATGAT	132

Physical clone: Exons were predicted by homology and the intron/exon boundaries were determined using standard genetic rules. Exons were further selected and refined by means of similarity determination using multiple BLAST (for example, tBlastN, BlastX, and BlastN) searches, and, in some instances, GeneScan and Grail. Expressed sequences from both public and proprietary databases were also added when available to further define and complete the gene sequence. The DNA sequence was then manually corrected for apparent inconsistencies thereby obtaining the sequences encoding the full-length protein.

Table 13B. Physical Clones for PCR products

NOVX Clone	Clone
NOV1a	Proprietary clones: 145150175, 145150395, 145150392, 145145203, 145150171, 145150168, 137114011
NOV2a	Physical clones: 107029754, AC078825, AC083812
NOV3	Physical clones: 134899552, AC005230
NOV4	Genomic clone: ba568g11
NOV5	Genomic clone: AC008774
NOV6	Bacterial clone: 111865::GMAC073364 A.698299.A2
NOV7	Physical clone: 106973211, AC015855.4

NOV8	Physical clone: 88091010, AL109932.3, AL360269.3, AL356323.6
NOV10	Proprietary clones: 140488852, 133419352, 141920635
NOV11a	Genomic clone: AC026125
NOV12	Genomic clone: AC011199

Example 2. Quantitative expression analysis of clones in various tissues and cells

The quantitative expression of various clones was assessed using microtiter plates containing RNA samples from a variety of normal and pathology-derived cells, cell lines and tissues using real time quantitative PCR (RTQ PCR). RTQ PCR was performed on an Applied Biosystems ABI PRISM® 7700 or an ABI PRISM® 7900 HT Sequence Detection System. Various collections of samples are assembled on the plates, and referred to as Panel 1 (containing normal tissues and cancer cell lines), Panel 2 (containing samples derived from tissues from normal and cancer sources), Panel 3 (containing cancer cell lines), Panel 4 (containing cells and cell lines from normal tissues and cells related to inflammatory conditions), Panel 5D/5I (containing human tissues and cell lines with an emphasis on metabolic diseases), AI_comprehensive_panel (containing normal tissue and samples from autoinflammatory diseases), Panel CNSD.01 (containing samples from normal and diseased brains) and CNS_neurodegeneration_panel (containing samples from normal and Alzheimer's diseased brains).

RNA integrity from all samples is controlled for quality by visual assessment of agarose gel electropherograms using 28S and 18S ribosomal RNA staining intensity ratio as a guide (2:1 to 2.5:1 28s:18s) and the absence of low molecular weight RNAs that would be indicative of degradation products. Samples are controlled against genomic DNA contamination by RTQ PCR reactions run in the absence of reverse transcriptase using probe and primer sets designed to amplify across the span of a single exon.

First, the RNA samples were normalized to reference nucleic acids such as constitutively expressed genes (for example, β -actin and GAPDH). Normalized RNA (5 μ l) was converted to cDNA and analyzed by RTQ-PCR using One Step RT-PCR Master Mix Reagents (Applied Biosystems; Catalog No. 4309169) and gene-specific primers according to the manufacturer's instructions.

In other cases, non-normalized RNA samples were converted to single strand cDNA (sscDNA) using Superscript II (Invitrogen Corporation; Catalog No. 18064-147) and random hexamers according to the manufacturer's instructions. Reactions containing up to 10 μ g of total RNA were performed in a volume of 20 μ l and incubated for 60 minutes at 42°C. This reaction can be scaled up to 50 μ g of total RNA in a final volume of 100 μ l. sscDNA samples are then normalized to reference nucleic acids as described previously, using 1X TaqMan®

Universal Master mix (Applied Biosystems; catalog No. 4324020), following the manufacturer's instructions.

Probes and primers were designed for each assay according to Applied Biosystems Primer Express Software package (version I for Apple Computer's Macintosh Power PC) or a similar algorithm using the target sequence as input. Default settings were used for reaction conditions and the following parameters were set before selecting primers: primer concentration = 250 nM, primer melting temperature (T_m) range = 58°-60°C, primer optimal T_m = 59°C, maximum primer difference = 2°C, probe does not have 5'G, probe T_m must be 10°C greater than primer T_m , amplicon size 75bp to 100bp. The probes and primers selected (see below) were synthesized by Synthegen (Houston, TX, USA). Probes were double purified by HPLC to remove uncoupled dye and evaluated by mass spectroscopy to verify coupling of reporter and quencher dyes to the 5' and 3' ends of the probe, respectively. Their final concentrations were: forward and reverse primers, 900nM each, and probe, 200nM.

PCR conditions: When working with RNA samples, normalized RNA from each tissue and each cell line was spotted in each well of either a 96 well or a 384-well PCR plate (Applied Biosystems). PCR cocktails included either a single gene specific probe and primers set, or two multiplexed probe and primers sets (a set specific for the target clone and another gene-specific set multiplexed with the target probe). PCR reactions were set up using TaqMan® One-Step RT-PCR Master Mix (Applied Biosystems, Catalog No. 4313803) following manufacturer's instructions. Reverse transcription was performed at 48°C for 30 minutes followed by amplification/PCR cycles as follows: 95°C 10 min, then 40 cycles of 95°C for 15 seconds, 60°C for 1 minute. Results were recorded as CT values (cycle at which a given sample crosses a threshold level of fluorescence) using a log scale, with the difference in RNA concentration between a given sample and the sample with the lowest CT value being represented as 2 to the power of delta CT. The percent relative expression is then obtained by taking the reciprocal of this RNA difference and multiplying by 100.

When working with sscDNA samples, normalized sscDNA was used as described previously for RNA samples. PCR reactions containing one or two sets of probe and primers were set up as described previously, using 1X TaqMan® Universal Master mix (Applied Biosystems; catalog No. 4324020), following the manufacturer's instructions. PCR amplification was performed as follows: 95°C 10 min, then 40 cycles of 95°C for 15 seconds, 60°C for 1 minute. Results were analyzed and processed as described previously.

Panels 1, 1.1, 1.2, and 1.3D

The plates for Panels 1, 1.1, 1.2 and 1.3D include 2 control wells (genomic DNA control and chemistry control) and 94 wells containing cDNA from various samples. The samples in these panels are broken into 2 classes: samples derived from cultured cell lines and samples derived from primary normal tissues. The cell lines are derived from cancers of the following types: lung cancer, breast cancer, melanoma, colon cancer, prostate cancer, CNS cancer, squamous cell carcinoma, ovarian cancer, liver cancer, renal cancer, gastric cancer and pancreatic cancer. Cell lines used in these panels are widely available through the American Type Culture Collection (ATCC), a repository for cultured cell lines, and were cultured using the conditions recommended by the ATCC. The normal tissues found on these panels are comprised of samples derived from all major organ systems from single adult individuals or fetuses. These samples are derived from the following organs: adult skeletal muscle, fetal skeletal muscle, adult heart, fetal heart, adult kidney, fetal kidney, adult liver, fetal liver, adult lung, fetal lung, various regions of the brain, the spleen, bone marrow, lymph node, pancreas, salivary gland, pituitary gland, adrenal gland, spinal cord, thymus, stomach, small intestine, colon, bladder, trachea, breast, ovary, uterus, placenta, prostate, testis and adipose.

In the results for Panels 1, 1.1, 1.2 and 1.3D, the following abbreviations are used:

ca. = carcinoma,
 * = established from metastasis,
 met = metastasis,
 s cell var = small cell variant,
 non-s = non-sm = non-small,
 squam = squamous,
 pl. eff = pl effusion = pleural effusion,
 glio = glioma,
 astro = astrocytoma, and
 neuro = neuroblastoma.

General_screening_panel_v1.4

The plates for Panel 1.4 include 2 control wells (genomic DNA control and chemistry control) and 94 wells containing cDNA from various samples. The samples in Panel 1.4 are broken into 2 classes: samples derived from cultured cell lines and samples derived from primary normal tissues. The cell lines are derived from cancers of the following types: lung cancer, breast cancer, melanoma, colon cancer, prostate cancer, CNS cancer, squamous cell carcinoma, ovarian cancer, liver cancer, renal cancer, gastric cancer and pancreatic cancer. Cell lines used in Panel 1.4 are widely available through the American Type Culture Collection (ATCC), a repository for cultured cell lines, and were cultured using the conditions

recommended by the ATCC. The normal tissues found on Panel 1.4 are comprised of pools of samples derived from all major organ systems from 2 to 5 different adult individuals or fetuses. These samples are derived from the following organs: adult skeletal muscle, fetal skeletal muscle, adult heart, fetal heart, adult kidney, fetal kidney, adult liver, fetal liver, adult lung, fetal lung, various regions of the brain, the spleen, bone marrow, lymph node, pancreas, salivary gland, pituitary gland, adrenal gland, spinal cord, thymus, stomach, small intestine, colon, bladder, trachea, breast, ovary, uterus, placenta, prostate, testis and adipose.

Abbreviations are as described for Panels 1, 1.1, 1.2, and 1.3D.

Panels 2D and 2.2

The plates for Panels 2D and 2.2 generally include 2 control wells and 94 test samples composed of RNA or cDNA isolated from human tissue procured by surgeons working in close cooperation with the National Cancer Institute's Cooperative Human Tissue Network (CHTN) or the National Disease Research Initiative (NDRI). The tissues are derived from human malignancies and in cases where indicated many malignant tissues have "matched margins" obtained from noncancerous tissue just adjacent to the tumor. These are termed normal adjacent tissues and are denoted "NAT" in the results below. The tumor tissue and the "matched margins" are evaluated by two independent pathologists (the surgical pathologists and again by a pathologist at NDRI or CHTN). This analysis provides a gross histopathological assessment of tumor differentiation grade. Moreover, most samples include the original surgical pathology report that provides information regarding the clinical stage of the patient. These matched margins are taken from the tissue surrounding (i.e. immediately proximal) to the zone of surgery (designated "NAT", for normal adjacent tissue, in Table RR). In addition, RNA and cDNA samples were obtained from various human tissues derived from autopsies performed on elderly people or sudden death victims (accidents, etc.). These tissues were ascertained to be free of disease and were purchased from various commercial sources such as Clontech (Palo Alto, CA), Research Genetics, and Invitrogen.

Panel 3D

The plates of Panel 3D are comprised of 94 cDNA samples and two control samples. Specifically, 92 of these samples are derived from cultured human cancer cell lines, 2 samples of human primary cerebellar tissue and 2 controls. The human cell lines are generally obtained from ATCC (American Type Culture Collection), NCI or the German tumor cell bank and fall into the following tissue groups: Squamous cell carcinoma of the tongue, breast cancer, prostate cancer, melanoma, epidermoid carcinoma, sarcomas, bladder carcinomas, pancreatic

cancers, kidney cancers, leukemias/lymphomas, ovarian/uterine/cervical, gastric, colon, lung and CNS cancer cell lines. In addition, there are two independent samples of cerebellum. These cells are all cultured under standard recommended conditions and RNA extracted using the standard procedures. The cell lines in panel 3D and 1.3D are of the most common cell lines used in the scientific literature.

Panels 4D, 4R, and 4.1D

Panel 4 includes samples on a 96 well plate (2 control wells, 94 test samples) composed of RNA (Panel 4R) or cDNA (Panels 4D/4.1D) isolated from various human cell lines or tissues related to inflammatory conditions. Total RNA from control normal tissues such as colon and lung (Stratagene, La Jolla, CA) and thymus and kidney (Clontech) was employed. Total RNA from liver tissue from cirrhosis patients and kidney from lupus patients was obtained from BioChain (Biochain Institute, Inc., Hayward, CA). Intestinal tissue for RNA preparation from patients diagnosed as having Crohn's disease and ulcerative colitis was obtained from the National Disease Research Interchange (NDRI) (Philadelphia, PA).

Astrocytes, lung fibroblasts, dermal fibroblasts, coronary artery smooth muscle cells, small airway epithelium, bronchial epithelium, microvascular dermal endothelial cells, microvascular lung endothelial cells, human pulmonary aortic endothelial cells, human umbilical vein endothelial cells were all purchased from Clonetics (Walkersville, MD) and grown in the media supplied for these cell types by Clonetics. These primary cell types were activated with various cytokines or combinations of cytokines for 6 and/or 12-14 hours, as indicated. The following cytokines were used; IL-1 beta at approximately 1-5ng/ml, TNF alpha at approximately 5-10ng/ml, IFN gamma at approximately 20-50ng/ml, IL-4 at approximately 5-10ng/ml, IL-9 at approximately 5-10ng/ml, IL-13 at approximately 5-10ng/ml. Endothelial cells were sometimes starved for various times by culture in the basal media from Clonetics with 0.1% serum.

Mononuclear cells were prepared from blood of employees at CuraGen Corporation, using Ficoll. LAK cells were prepared from these cells by culture in DMEM 5% FCS (Hyclone), 100µM non essential amino acids (Gibco/Life Technologies, Rockville, MD), 1mM sodium pyruvate (Gibco), mercaptoethanol 5.5×10^{-5} M (Gibco), and 10mM Hepes (Gibco) and Interleukin 2 for 4-6 days. Cells were then either activated with 10-20ng/ml PMA and 1-2µg/ml ionomycin, IL-12 at 5-10ng/ml, IFN gamma at 20-50ng/ml and IL-18 at 5-10ng/ml for 6 hours. In some cases, mononuclear cells were cultured for 4-5 days in DMEM 5% FCS (Hyclone), 100µM non essential amino acids (Gibco), 1mM sodium pyruvate

(Gibco), mercaptoethanol 5.5×10^{-5} M (Gibco), and 10mM Hepes (Gibco) with PHA (phytohemagglutinin) or PWM (pokeweed mitogen) at approximately 5µg/ml. Samples were taken at 24, 48 and 72 hours for RNA preparation. MLR (mixed lymphocyte reaction) samples were obtained by taking blood from two donors, isolating the mononuclear cells using Ficoll and mixing the isolated mononuclear cells 1:1 at a final concentration of approximately 2×10^6 cells/ml in DMEM 5% FCS (Hyclone), 100µM non essential amino acids (Gibco), 1mM sodium pyruvate (Gibco), mercaptoethanol (5.5×10^{-5} M) (Gibco), and 10mM Hepes (Gibco). The MLR was cultured and samples taken at various time points ranging from 1- 7 days for RNA preparation.

Monocytes were isolated from mononuclear cells using CD14 Miltenyi Beads, +ve VS selection columns and a Vario Magnet according to the manufacturer's instructions. Monocytes were differentiated into dendritic cells by culture in DMEM 5% fetal calf serum (FCS) (Hyclone, Logan, UT), 100µM non essential amino acids (Gibco), 1mM sodium pyruvate (Gibco), mercaptoethanol 5.5×10^{-5} M (Gibco), and 10mM Hepes (Gibco), 50ng/ml GM-CSF and 5ng/ml IL-4 for 5-7 days. Macrophages were prepared by culture of monocytes for 5-7 days in DMEM 5% FCS (Hyclone), 100µM non essential amino acids (Gibco), 1mM sodium pyruvate (Gibco), mercaptoethanol 5.5×10^{-5} M (Gibco), 10mM Hepes (Gibco) and 10% AB Human Serum or MCSF at approximately 50ng/ml. Monocytes, macrophages and dendritic cells were stimulated for 6 and 12-14 hours with lipopolysaccharide (LPS) at 100ng/ml. Dendritic cells were also stimulated with anti-CD40 monoclonal antibody (Pharmingen) at 10µg/ml for 6 and 12-14 hours.

CD4 lymphocytes, CD8 lymphocytes and NK cells were also isolated from mononuclear cells using CD4, CD8 and CD56 Miltenyi beads, positive VS selection columns and a Vario Magnet according to the manufacturer's instructions. CD45RA and CD45RO CD4 lymphocytes were isolated by depleting mononuclear cells of CD8, CD56, CD14 and CD19 cells using CD8, CD56, CD14 and CD19 Miltenyi beads and positive selection. CD45RO beads were then used to isolate the CD45RO CD4 lymphocytes with the remaining cells being CD45RA CD4 lymphocytes. CD45RA CD4, CD45RO CD4 and CD8 lymphocytes were placed in DMEM 5% FCS (Hyclone), 100µM non essential amino acids (Gibco), 1mM sodium pyruvate (Gibco), mercaptoethanol 5.5×10^{-5} M (Gibco), and 10mM Hepes (Gibco) and plated at 10^6 cells/ml onto Falcon 6 well tissue culture plates that had been coated overnight with 0.5µg/ml anti-CD28 (Pharmingen) and 3µg/ml anti-CD3 (OKT3, ATCC) in PBS. After 6 and 24 hours, the cells were harvested for RNA preparation. To prepare chronically activated CD8 lymphocytes, we activated the isolated CD8 lymphocytes for 4 days on anti-CD28 and

anti-CD3 coated plates and then harvested the cells and expanded them in DMEM 5% FCS (Hyclone), 100µM non essential amino acids (Gibco), 1mM sodium pyruvate (Gibco), mercaptoethanol 5.5×10^{-5} M (Gibco), and 10mM Hepes (Gibco) and IL-2. The expanded CD8 cells were then activated again with plate bound anti-CD3 and anti-CD28 for 4 days and expanded as before. RNA was isolated 6 and 24 hours after the second activation and after 4 days of the second expansion culture. The isolated NK cells were cultured in DMEM 5% FCS (Hyclone), 100µM non essential amino acids (Gibco), 1mM sodium pyruvate (Gibco), mercaptoethanol 5.5×10^{-5} M (Gibco), and 10mM Hepes (Gibco) and IL-2 for 4-6 days before RNA was prepared.

To obtain B cells, tonsils were procured from NDRI. The tonsil was cut up with sterile dissecting scissors and then passed through a sieve. Tonsil cells were then spun down and resuspended at 10^6 cells/ml in DMEM 5% FCS (Hyclone), 100µM non essential amino acids (Gibco), 1mM sodium pyruvate (Gibco), mercaptoethanol 5.5×10^{-5} M (Gibco), and 10mM Hepes (Gibco). To activate the cells, we used PWM at 5µg/ml or anti-CD40 (Pharmingen) at approximately 10µg/ml and IL-4 at 5-10ng/ml. Cells were harvested for RNA preparation at 24, 48 and 72 hours.

To prepare the primary and secondary Th1/Th2 and Tr1 cells, six-well Falcon plates were coated overnight with 10µg/ml anti-CD28 (Pharmingen) and 2µg/ml OKT3 (ATCC), and then washed twice with PBS. Umbilical cord blood CD4 lymphocytes (Poietic Systems, German Town, MD) were cultured at 10^5 - 10^6 cells/ml in DMEM 5% FCS (Hyclone), 100µM non essential amino acids (Gibco), 1mM sodium pyruvate (Gibco), mercaptoethanol 5.5×10^{-5} M (Gibco), 10mM Hepes (Gibco) and IL-2 (4ng/ml). IL-12 (5ng/ml) and anti-IL4 (1µg/ml) were used to direct to Th1, while IL-4 (5ng/ml) and anti-IFN gamma (1µg/ml) were used to direct to Th2 and IL-10 at 5ng/ml was used to direct to Tr1. After 4-5 days, the activated Th1, Th2 and Tr1 lymphocytes were washed once in DMEM and expanded for 4-7 days in DMEM 5% FCS (Hyclone), 100µM non essential amino acids (Gibco), 1mM sodium pyruvate (Gibco), mercaptoethanol 5.5×10^{-5} M (Gibco), 10mM Hepes (Gibco) and IL-2 (1ng/ml). Following this, the activated Th1, Th2 and Tr1 lymphocytes were re-stimulated for 5 days with anti-CD28/OKT3 and cytokines as described above, but with the addition of anti-CD95L (1µg/ml) to prevent apoptosis. After 4-5 days, the Th1, Th2 and Tr1 lymphocytes were washed and then expanded again with IL-2 for 4-7 days. Activated Th1 and Th2 lymphocytes were maintained in this way for a maximum of three cycles. RNA was prepared from primary and secondary Th1, Th2 and Tr1 after 6 and 24 hours following the second and third

activations with plate bound anti-CD3 and anti-CD28 mAbs and 4 days into the second and third expansion cultures in Interleukin 2.

The following leukocyte cells lines were obtained from the ATCC: Ramos, EOL-1, KU-812. EOL cells were further differentiated by culture in 0.1mM dbcAMP at 5×10^5 cells/ml for 8 days, changing the media every 3 days and adjusting the cell concentration to 5×10^5 cells/ml. For the culture of these cells, we used DMEM or RPMI (as recommended by the ATCC), with the addition of 5% FCS (Hyclone), 100 μ M non essential amino acids (Gibco), 1mM sodium pyruvate (Gibco), mercaptoethanol 5.5×10^{-5} M (Gibco), 10mM Hepes (Gibco). RNA was either prepared from resting cells or cells activated with PMA at 10ng/ml and ionomycin at 1 μ g/ml for 6 and 14 hours. Keratinocyte line CCD106 and an airway epithelial tumor line NCI-H292 were also obtained from the ATCC. Both were cultured in DMEM 5% FCS (Hyclone), 100 μ M non essential amino acids (Gibco), 1mM sodium pyruvate (Gibco), mercaptoethanol 5.5×10^{-5} M (Gibco), and 10mM Hepes (Gibco). CCD1106 cells were activated for 6 and 14 hours with approximately 5 ng/ml TNF alpha and 1ng/ml IL-1 beta, while NCI-H292 cells were activated for 6 and 14 hours with the following cytokines: 5ng/ml IL-4, 5ng/ml IL-9, 5ng/ml IL-13 and 25ng/ml IFN gamma.

For these cell lines and blood cells, RNA was prepared by lysing approximately 10^7 cells/ml using Trizol (Gibco BRL). Briefly, 1/10 volume of bromochloropropane (Molecular Research Corporation) was added to the RNA sample, vortexed and after 10 minutes at room temperature, the tubes were spun at 14,000 rpm in a Sorvall SS34 rotor. The aqueous phase was removed and placed in a 15ml Falcon Tube. An equal volume of isopropanol was added and left at -20°C overnight. The precipitated RNA was spun down at 9,000 rpm for 15 min in a Sorvall SS34 rotor and washed in 70% ethanol. The pellet was redissolved in 300 μ l of RNase-free water and 35 μ l buffer (Promega) 5 μ l DTT, 7 μ l RNasin and 8 μ l DNase were added. The tube was incubated at 37°C for 30 minutes to remove contaminating genomic DNA, extracted once with phenol chloroform and re-precipitated with 1/10 volume of 3M sodium acetate and 2 volumes of 100% ethanol. The RNA was spun down and placed in RNase free water. RNA was stored at -80°C.

AI_comprehensive panel_v1.0

The plates for AI_comprehensive panel_v1.0 include two control wells and 89 test samples comprised of cDNA isolated from surgical and postmortem human tissues obtained from the Backus Hospital and Clinomics (Frederick, MD). Total RNA was extracted from

tissue samples from the Backus Hospital in the Facility at CuraGen. Total RNA from other tissues was obtained from Clinomics.

Joint tissues including synovial fluid, synovium, bone and cartilage were obtained from patients undergoing total knee or hip replacement surgery at the Backus Hospital. Tissue samples were immediately snap frozen in liquid nitrogen to ensure that isolated RNA was of optimal quality and not degraded. Additional samples of osteoarthritis and rheumatoid arthritis joint tissues were obtained from Clinomics. Normal control tissues were supplied by Clinomics and were obtained during autopsy of trauma victims.

Surgical specimens of psoriatic tissues and adjacent matched tissues were provided as total RNA by Clinomics. Two male and two female patients were selected between the ages of 25 and 47. None of the patients were taking prescription drugs at the time samples were isolated.

Surgical specimens of diseased colon from patients with ulcerative colitis and Crohns disease and adjacent matched tissues were obtained from Clinomics. Bowel tissue from three female and three male Crohn's patients between the ages of 41-69 were used. Two patients were not on prescription medication while the others were taking dexamethasone, phenobarbital, or tylenol. Ulcerative colitis tissue was from three male and four female patients. Four of the patients were taking lebid and two were on phenobarbital.

Total RNA from post mortem lung tissue from trauma victims with no disease or with emphysema, asthma or COPD was purchased from Clinomics. Emphysema patients ranged in age from 40-70 and all were smokers, this age range was chosen to focus on patients with cigarette-linked emphysema and to avoid those patients with alpha-1 anti-trypsin deficiencies. Asthma patients ranged in age from 36-75, and excluded smokers to prevent those patients that could also have COPD. COPD patients ranged in age from 35-80 and included both smokers and non-smokers. Most patients were taking corticosteroids, and bronchodilators.

In the labels employed to identify tissues in the AI_comprehensive panel_v1.0 panel, the following abbreviations are used:

AI = Autoimmunity
Syn = Synovial
Normal = No apparent disease
Rep22 /Rep20 = individual patients
RA = Rheumatoid arthritis
Backus = From Backus Hospital
OA = Osteoarthritis
(SS) (BA) (MF) = Individual patients
Adj = Adjacent tissue

Match control = adjacent tissues
 -M = Male
 -F = Female
 COPD = Chronic obstructive pulmonary disease

5

Panels 5D and 5I

The plates for Panel 5D and 5I include two control wells and a variety of cDNAs isolated from human tissues and cell lines with an emphasis on metabolic diseases. Metabolic tissues were obtained from patients enrolled in the Gestational Diabetes study. Cells were
 10 obtained during different stages in the differentiation of adipocytes from human mesenchymal stem cells. Human pancreatic islets were also obtained.

In the Gestational Diabetes study subjects are young (18 - 40 years), otherwise healthy women with and without gestational diabetes undergoing routine (elective) Caesarean section. After delivery of the infant, when the surgical incisions were being repaired/closed, the
 15 obstetrician removed a small sample.

Patient 2: Diabetic Hispanic, overweight, not on insulin
 Patient 7-9: Nondiabetic Caucasian and obese (BMI>30)
 Patient 10: Diabetic Hispanic, overweight, on insulin
 Patient 11: Nondiabetic African American and overweight
 20 Patient 12: Diabetic Hispanic on insulin

Adipocyte differentiation was induced in donor progenitor cells obtained from Osirus (a division of Clonetics/BioWhittaker) in triplicate, except for Donor 3U which had only two replicates. Scientists at Clonetics isolated, grew and differentiated human mesenchymal stem cells (HuMSCs) for CuraGen based on the published protocol found in Mark F. Pittenger, et
 25 al., Multilineage Potential of Adult Human Mesenchymal Stem Cells Science Apr 2 1999: 143-147. Clonetics provided Trizol lysates or frozen pellets suitable for mRNA isolation and ds cDNA production. A general description of each donor is as follows:

Donor 2 and 3 U: Mesenchymal Stem cells, Undifferentiated Adipose
 Donor 2 and 3 AM: Adipose, AdiposeMidway Differentiated
 30 Donor 2 and 3 AD: Adipose, Adipose Differentiated

Human cell lines were generally obtained from ATCC (American Type Culture Collection), NCI or the German tumor cell bank and fall into the following tissue groups: kidney proximal convoluted tubule, uterine smooth muscle cells, small intestine, liver HepG2 cancer cells, heart primary stromal cells, and adrenal cortical adenoma cells. These cells are all
 35 cultured under standard recommended conditions and RNA extracted using the standard procedures. All samples were processed at CuraGen to produce single stranded cDNA.

Panel 5I contains all samples previously described with the addition of pancreatic islets from a 58 year old female patient obtained from the Diabetes Research Institute at the University of Miami School of Medicine. Islet tissue was processed to total RNA at an outside source and delivered to CuraGen for addition to panel 5I.

5 In the labels employed to identify tissues in the 5D and 5I panels, the following abbreviations are used:

GO Adipose = Greater Omentum Adipose
 SK = Skeletal Muscle
 UT = Uterus
 10 PL = Placenta
 AD = Adipose Differentiated
 AM = Adipose Midway Differentiated
 U = Undifferentiated Stem Cells

15 **Panel CNSD.01**

The plates for Panel CNSD.01 include two control wells and 94 test samples comprised of cDNA isolated from postmortem human brain tissue obtained from the Harvard Brain Tissue Resource Center. Brains are removed from calvaria of donors between 4 and 24 hours after death, sectioned by neuroanatomists, and frozen at -80°C in liquid nitrogen vapor.
 20 All brains are sectioned and examined by neuropathologists to confirm diagnoses with clear associated neuropathology.

Disease diagnoses are taken from patient records. The panel contains two brains from each of the following diagnoses: Alzheimer's disease, Parkinson's disease, Huntington's disease, Progressive Supranuclear Palsy, Depression, and "Normal controls". Within each of
 25 these brains, the following regions are represented: cingulate gyrus, temporal pole, globus pallidus, substantia nigra, Brodman Area 4 (primary motor strip), Brodman Area 7 (parietal cortex), Brodman Area 9 (prefrontal cortex), and Brodman area 17 (occipital cortex). Not all brain regions are represented in all cases; e.g., Huntington's disease is characterized in part by neurodegeneration in the globus pallidus, thus this region is impossible to obtain from
 30 confirmed Huntington's cases. Likewise Parkinson's disease is characterized by degeneration of the substantia nigra making this region more difficult to obtain. Normal control brains were examined for neuropathology and found to be free of any pathology consistent with neurodegeneration.

In the labels employed to identify tissues in the CNS panel, the following abbreviations
 35 are used:

PSP = Progressive supranuclear palsy
 Sub Nigra = Substantia nigra
 Glob Palladus= Globus palladus
 Temp Pole = Temporal pole
 Cing Gyr = Cingulate gyrus
 BA 4 = Brodman Area 4

Panel CNS_Neurodegeneration_V1.0

The plates for Panel CNS_Neurodegeneration_V1.0 include two control wells and 47 test samples comprised of cDNA isolated from postmortem human brain tissue obtained from the Harvard Brain Tissue Resource Center (McLean Hospital) and the Human Brain and Spinal Fluid Resource Center (VA Greater Los Angeles Healthcare System). Brains are removed from calvaria of donors between 4 and 24 hours after death, sectioned by neuroanatomists, and frozen at -80°C in liquid nitrogen vapor. All brains are sectioned and examined by neuropathologists to confirm diagnoses with clear associated neuropathology.

Disease diagnoses are taken from patient records. The panel contains six brains from Alzheimer's disease (AD) patients, and eight brains from "Normal controls" who showed no evidence of dementia prior to death. The eight normal control brains are divided into two categories: Controls with no dementia and no Alzheimer's like pathology (Controls) and controls with no dementia but evidence of severe Alzheimer's like pathology, (specifically senile plaque load rated as level 3 on a scale of 0-3; 0 = no evidence of plaques, 3 = severe AD senile plaque load). Within each of these brains, the following regions are represented: hippocampus, temporal cortex (Brodman Area 21), parietal cortex (Brodman area 7), and occipital cortex (Brodman area 17). These regions were chosen to encompass all levels of neurodegeneration in AD. The hippocampus is a region of early and severe neuronal loss in AD; the temporal cortex is known to show neurodegeneration in AD after the hippocampus; the parietal cortex shows moderate neuronal death in the late stages of the disease; the occipital cortex is spared in AD and therefore acts as a "control" region within AD patients. Not all brain regions are represented in all cases.

In the labels employed to identify tissues in the CNS_Neurodegeneration_V1.0 panel, the following abbreviations are used:

AD = Alzheimer's disease brain; patient was demented and showed AD-like pathology upon autopsy
 Control = Control brains; patient not demented, showing no neuropathology
 Control (Path) = Control brains; pateint not demented but showing sever AD-like pathology
 SupTemporal Ctx = Superior Temporal Cortex
 Inf Temporal Ctx = Inferior Temporal Cortex

NOV1b, NOV1c

Expression of NOV1b and NOV1c was assessed using the primer-probe sets Ag1848, Ag2263, Ag2422 and Ag1522, described in Tables 14, 15, 16 and 17. Results of the RTQ-PCR runs are shown in Tables 18, 19, 20, 21, 22, 23 and 24.

Table 14. Probe Name Ag1848

Primers	Sequences	Length	Start Position	SEQ ID NO:
Forward	5' -TGACTTCGACACAGACATCACT-3'	22	1234	133
Probe	TET-5' -ACTCATCTGCTGCCCTGACTGGTG-3' -TAMRA	24	1257	134
Reverse	5' -CCTTGCCGTCTTAAAGTTGAC-3'	21	1292	135

Table 15. Probe Name Ag2263

Primers	Sequences	Length	Start Position	SEQ ID NO:
Forward	5' -TGACTTCGACACAGACATCACT-3'	22	1234	136
Probe	TET-5' -ACTCATCTGCTGCCCTGACTGGTG-3' -TAMRA	24	1257	137
Reverse	5' -CCTTGCCGTCTTAAAGTTGAC-3'	21	1292	138

Table 16. Probe Name Ag2422

Primers	Sequences	Length	Start Position	SEQ ID NO:
Forward	5' -GGCTCCCTGGACACTCTCT-3'	19	2522	139
Probe	TET-5' -CTGTCACCACCCAGCTGGGACCTTAT-3' -TAMRA	26	2559	140
Reverse	5' -TGGACAGTGGGATCTTGAAG-3'	20	2587	141

Table 17. Probe Name Ag1522

Primers	Sequences	Length	Start Position	SEQ ID NO:
Forward	5' -TGACTTCGACACAGACATCACT-3'	22	1234	142
Probe	TET-5' -ACTCATCTGCTGCCCTGACTGGTG-3' -TAMRA	24	1257	143
Reverse	5' -CCTTGCCGTCTTAAAGTTGAC-3'	21	1292	144

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Table 18. CNS_neurodegeneration_v1.0

Tissue Name	Rel. Exp.(%) Ag1848, Run 207776125	Rel. Exp.(%) Ag2263, Run 219933384	Rel. Exp.(%) Ag2263, Run 224115886	Rel. Exp.(%) Ag2422, Run 206262709	Rel. Exp.(%) Ag2422, Run 230512499
AD 1 Hippo	28.3	39.0	19.3	21.3	16.6
AD 2 Hippo	37.9	45.1	23.5	38.7	40.1

AD 3 Hippo	12.0	20.6	13.9	14.9	13.0
AD 4 Hippo	17.7	27.2	9.0	13.3	16.4
AD 5 Hippo	45.4	60.3	8.1	57.8	59.0
AD 6 Hippo	66.9	96.6	70.2	95.9	66.0
Control 2 Hippo	43.2	81.2	67.8	46.0	48.3
Control 4 Hippo	34.2	36.6	38.7	30.4	27.5
Control (Path) 3 Hippo	3.9	11.0	4.6	12.7	12.1
AD 1 Temporal Ctx	47.0	79.0	69.7	40.6	27.2
AD 2 Temporal Ctx	49.3	61.6	70.7	39.8	50.7
AD 3 Temporal Ctx	14.5	20.7	15.3	15.7	14.5
AD 4 Temporal Ctx	41.5	53.6	31.9	36.3	39.0
AD 5 Inf Temporal Ctx	77.9	95.9	72.2	88.9	100.0
AD 5 Sup Temporal Ctx	40.9	57.4	3.7	57.0	69.3
AD 6 Inf Temporal Ctx	84.1	99.3	100.0	74.2	83.5
AD 6 Sup Temporal Ctx	58.2	64.6	81.8	71.7	61.1
Control 1 Temporal Ctx	17.9	18.0	21.5	11.3	16.5
Control 2 Temporal Ctx	45.7	39.8	66.4	44.8	55.1
Control 3 Temporal Ctx	14.7	21.8	22.7	15.6	13.5
Control 3 Temporal Ctx	23.2	21.5	23.8	19.1	24.1
Control (Path) 1 Temporal Ctx	46.0	39.8	19.3	40.3	51.1
Control (Path) 2 Temporal Ctx	24.7	40.6	23.7	21.8	24.0
Control (Path) 3 Temporal Ctx	6.0	8.2	8.0	7.7	7.3
Control (Path) 4 Temporal Ctx	32.1	29.5	31.0	24.0	18.6
AD 1 Occipital Ctx	24.1	48.0	5.5	26.4	13.7
AD 2 Occipital Ctx (Missing)	0.0	0.0	0.0	0.0	0.0
AD 3 Occipital Ctx	19.2	25.3	20.4	18.2	18.8
AD 4 Occipital Ctx	30.1	58.2	30.6	23.3	30.8
AD 5 Occipital Ctx	6.0	39.0	8.5	26.8	23.0
AD 5 Occipital Ctx	43.2	51.8	53.6	50.3	47.6
Control 1 Occipital Ctx	14.6	22.2	19.1	12.8	13.4
Control 2 Occipital Ctx	66.9	85.9	94.6	76.3	70.2
Control 3 Occipital Ctx	17.8	37.1	8.0	17.4	13.1
Control 4 Occipital Ctx	23.3	22.2	2.7	15.7	19.1
Control (Path) 1 Occipital Ctx	100.0	100.0	63.7	100.0	90.1
Control (Path) 2 Occipital Ctx	18.7	20.9	11.0	12.3	11.7
Control (Path) 3 Occipital	7.9	6.1	9.4	7.1	5.8

Ctx					
Control (Path) 4 Occipital Ctx	24.5	21.5	11.1	14.0	13.1
Control 1 Parietal Ctx	23.2	26.8	7.4	22.2	17.6
Control 2 Parietal Ctx	46.0	65.1	71.2	64.6	50.0
Control 3 Parietal Ctx	26.1	27.2	16.5	17.3	19.5
Control (Path) 1 Parietal Ctx	51.1	66.0	80.1	54.3	55.1
Control (Path) 2 Parietal Ctx	36.3	16.5	34.2	27.9	27.9
Control (Path) 3 Parietal Ctx	6.1	10.5	1.4	5.1	4.6
Control (Path) 4 Parietal Ctx	46.0	52.5	10.7	36.6	12.2

Table 19. Panel 1.2

Tissue Name	Rel. Exp.(%) Ag1522, Run 142131145	Tissue Name	Rel. Exp.(%) Ag1522, Run 142131145
Endothelial cells	1.2	Renal ca. 786-0	0.0
Heart (Fetal)	17.9	Renal ca. A498	0.3
Pancreas	0.7	Renal ca. RXF 393	0.2
Pancreatic ca. CAPAN 2	4.9	Renal ca. ACHN	0.1
Adrenal Gland	7.9	Renal ca. UO-31	0.5
Thyroid	0.1	Renal ca. TK-10	0.3
Salivary gland	2.5	Liver	2.4
Pituitary gland	0.1	Liver (fetal)	0.5
Brain (fetal)	0.2	Liver ca. (hepatoblast) HepG2	0.3
Brain (whole)	3.2	Lung	0.3
Brain (amygdala)	4.4	Lung (fetal)	0.4
Brain (cerebellum)	9.0	Lung ca. (small cell) LX-1	25.3
Brain (hippocampus)	18.9	Lung ca. (small cell) NCI- H69	43.8
Brain (thalamus)	15.7	Lung ca. (s.cell var.) SHP- 77	0.3
Cerebral Cortex	35.4	Lung ca. (large cell) NCI- H460	54.7
Spinal cord	1.6	Lung ca. (non-sm. cell) A549	0.3
glio/astro U87-MG	72.2	Lung ca. (non-s.cell) NCI- H23	2.4
glio/astro U-118-MG	3.1	Lung ca. (non-s.cell) HOP- 62	1.7
astrocytoma SW1783	0.3	Lung ca. (non-s.cl) NCI-	9.3

		H522	
neuro*; met SK-N-AS	36.3	Lung ca. (squam.) SW 900	1.5
astrocytoma SF-539	5.8	Lung ca. (squam.) NCI-H596	22.4
astrocytoma SNB-75	1.7	Mammary gland	1.4
glioma SNB-19	23.8	Breast ca.* (pl.ef) MCF-7	0.8
glioma U251	2.9	Breast ca.* (pl.ef) MDA-MB-231	0.1
glioma SF-295	100.0	Breast ca.* (pl. ef) T47D	18.4
Heart	31.6	Breast ca. BT-549	0.1
Skeletal Muscle	3.4	Breast ca. MDA-N	0.0
Bone marrow	0.2	Ovary	6.9
Thymus	0.2	Ovarian ca. OVCAR-3	1.7
Spleen	2.1	Ovarian ca. OVCAR-4	12.9
Lymph node	0.5	Ovarian ca. OVCAR-5	5.7
Colorectal	1.4	Ovarian ca. OVCAR-8	5.3
Stomach	1.3	Ovarian ca. IGROV-1	0.8
Small intestine	3.3	Ovarian ca. (ascites) SK-OV-3	5.4
Colon ca. SW480	0.8	Uterus	0.9
Colon ca.* SW620 (SW480 met)	2.2	Placenta	0.9
Colon ca. HT29	0.1	Prostate	10.0
Colon ca. HCT-116	7.5	Prostate ca.* (bone met) PC-3	0.1
Colon ca. CaCo-2	6.3	Testis	0.3
CC Well to Mod Diff (ODO3866)	3.0	Melanoma Hs688(A).T	21.2
Colon ca. HCC-2998	1.2	Melanoma* (met) Hs688(B).T	28.5
Gastric ca. (liver met) NCI-N87	24.7	Melanoma UACC-62	2.4
Bladder	12.8	Melanoma M14	0.1
Trachea	0.3	Melanoma LOX IMVI	0.1
Kidney	19.2	Melanoma* (met) SK-MEL-5	1.2
Kidney (fetal)	6.6		

Table 20. Panel 1.3D

Tissue Name	Rel. Exp.(%) Ag1522, Run 159601761	Rel. Exp.(%) Ag1848, Run 160201402	Rel. Exp.(%) Ag2263, Run 166011650	Rel. Exp.(%) Ag2422, Run 159319549
Liver adenocarcinoma	15.8	12.3	31.4	18.3
Pancreas	1.7	1.4	2.8	2.9

Pancreatic ca. CAPAN 2	6.7	4.6	21.6	5.5
Adrenal gland	3.9	2.0	3.5	3.0
Thyroid	1.7	1.5	0.0	2.5
Salivary gland	0.6	0.2	2.3	0.3
Pituitary gland	2.1	1.4	2.9	4.3
Brain (fetal)	1.4	1.1	3.5	1.1
Brain (whole)	28.7	13.5	43.2	10.4
Brain (amygdala)	16.8	13.0	31.2	18.6
Brain (cerebellum)	8.2	6.5	42.3	9.2
Brain (hippocampus)	60.7	47.6	16.8	51.8
Brain (substantia nigra)	8.9	5.2	32.3	6.8
Brain (thalamus)	40.1	22.2	62.0	19.8
Cerebral Cortex	25.9	18.4	36.6	14.3
Spinal cord	10.2	5.4	37.9	7.9
glio/astro U87-MG	43.2	34.6	100.0	48.6
glio/astro U-118-MG	10.2	8.0	6.4	7.5
astrocytoma SW1783	0.9	0.8	2.8	1.1
neuro*; met SK-N-AS	100.0	100.0	59.0	100.0
astrocytoma SF-539	9.7	8.3	17.7	9.0
astrocytoma SNB-75	12.9	12.1	8.4	12.1
glioma SNB-19	19.5	17.6	46.3	17.2
glioma U251	13.4	10.6	24.5	10.9
glioma SF-295	66.9	62.4	64.2	62.0
Heart (Fetal)	15.6	12.5	20.0	18.7
Heart	2.2	1.1	3.4	3.3
Skeletal muscle (Fetal)	22.2	14.0	6.7	19.3
Skeletal muscle	0.3	0.2	1.4	0.7
Bone marrow	0.7	0.3	0.4	0.8
Thymus	2.0	1.6	3.6	3.4
Spleen	7.9	5.6	4.5	5.9
Lymph node	2.6	1.9	2.7	2.1
Colorectal	4.7	9.2	12.8	10.3
Stomach	6.1	2.4	3.6	4.5
Small intestine	2.9	2.9	4.5	4.9
Colon ca. SW480	2.0	1.0	1.9	1.5
Colon ca.* SW620 (SW480 met)	1.0	1.2	2.0	2.1
Colon ca. HT29	0.1	0.1	0.0	0.1
Colon ca. HCT-116	4.2	2.9	4.7	5.6
Colon ca. CaCo-2	5.3	3.9	12.5	7.2
CC Well to Mod Diff (ODO3866)	14.8	17.3	19.8	23.5
Colon ca. HCC-2998	0.7	1.6	0.0	0.5

Gastric ca. (liver met) NCI-N87	21.9	22.8	19.1	25.7
Bladder	2.1	1.7	3.4	1.5
Trachea	12.2	6.8	1.6	13.8
Kidney	1.4	0.6	3.9	3.0
Kidney (fetal)	5.3	5.8	5.2	6.3
Renal ca. 786-0	0.1	0.0	0.0	0.0
Renal ca. A498	7.7	7.9	6.8	9.7
Renal ca. RXF 393	0.1	3.6	0.8	0.1
Renal ca. ACHN	0.0	0.0	0.0	0.0
Renal ca. UO-31	0.2	0.3	0.5	0.3
Renal ca. TK-10	0.1	0.0	0.0	0.0
Liver	0.3	0.1	0.0	0.6
Liver (fetal)	1.1	1.0	0.3	1.2
Liver ca. (hepatoblast) HepG2	0.2	0.0	0.8	0.3
Lung	8.2	9.4	4.1	10.3
Lung (fetal)	4.3	4.2	7.3	4.5
Lung ca. (small cell) LX-1	8.4	6.9	31.6	9.9
Lung ca. (small cell) NCI-H69	44.4	48.6	90.8	54.3
Lung ca. (s.cell var.) SHP-77	0.7	0.8	0.5	1.1
Lung ca. (large cell) NCI-H460	16.2	11.9	22.4	12.1
Lung ca. (non-sm. cell) A549	0.4	0.3	0.2	0.4
Lung ca. (non-s.cell) NCI-H23	2.0	0.9	3.3	1.2
Lung ca. (non-s.cell) HOP-62	0.4	0.9	1.6	0.7
Lung ca. (non-s.cl) NCI-H522	1.7	0.8	1.7	1.1
Lung ca. (squam.) SW 900	0.5	0.3	1.9	0.2
Lung ca. (squam.) NCI-H596	4.0	4.1	26.4	2.4
Mammary gland	6.3	4.4	3.0	2.8
Breast ca.* (pl.ef) MCF-7	1.1	0.4	1.5	0.9
Breast ca.* (pl.ef) MDA-MB-231	0.8	1.2	0.7	1.4
Breast ca.* (pl. ef) T47D	9.6	5.7	14.0	4.5
Breast ca. BT-549	0.2	0.3	0.2	0.3
Breast ca. MDA-N	0.0	0.0	0.0	0.0
Ovary	6.4	4.9	6.2	9.5
Ovarian ca. OVCAR-3	1.1	0.6	1.1	0.8
Ovarian ca. OVCAR-4	1.0	1.4	11.4	1.5
Ovarian ca. OVCAR-5	2.4	2.6	5.7	3.3
Ovarian ca. OVCAR-8	3.6	1.6	2.6	5.4
Ovarian ca. IGROV-1	0.6	0.2	0.7	0.2
Ovarian ca. (ascites) SK-OV-3	2.0	2.6	2.1	1.1
Uterus	2.7	1.3	3.9	4.2
Placenta	2.0	2.0	5.8	4.8

Prostate	4.4	2.5	3.4	5.4
Prostate ca.* (bone met) PC-3	0.1	0.1	0.2	0.0
Testis	8.1	5.5	3.5	6.4
Melanoma Hs688(A).T	31.6	25.0	59.5	27.4
Melanoma* (met) Hs688(B).T	46.0	17.1	87.1	28.5
Melanoma UACC-62	0.1	0.2	2.0	0.5
Melanoma M14	0.0	0.0	0.0	0.0
Melanoma LOX IMVI	0.1	0.2	0.0	0.1
Melanoma* (met) SK-MEL-5	0.9	0.9	1.7	0.6
Adipose	3.6	2.3	5.1	2.9

Table 21. Panel 2D

Tissue Name	Rel. Exp.(%) Ag1522, Run 145049854	Rel. Exp.(%) Ag1522, Run 145492337	Rel. Exp.(%) Ag1848, Run 160202834	Rel. Exp.(%) Ag2263, Run 165725935	Rel. Exp.(%) Ag2422, Run 159317774
Normal Colon	20.2	46.0	35.1	59.0	36.9
CC Well to Mod Diff (ODO3866)	15.3	45.1	22.5	21.8	21.3
CC Margin (ODO3866)	6.1	15.2	7.4	7.7	5.5
CC Gr.2 rectosigmoid (ODO3868)	7.0	8.2	5.8	5.9	13.2
CC Margin (ODO3868)	0.3	0.5	0.5	9.3	0.8
CC Mod Diff (ODO3920)	1.2	4.0	2.5	5.6	5.8
CC Margin (ODO3920)	3.0	4.7	4.1	5.4	7.2
CC Gr.2 ascend colon (ODO3921)	10.7	22.5	24.1	19.9	25.5
CC Margin (ODO3921)	3.6	4.3	7.3	5.6	5.8
CC from Partial Hepatectomy (ODO4309) Mets	12.1	19.9	20.7	19.3	27.0
Liver Margin (ODO4309)	0.4	3.6	2.4	2.6	3.3
Colon mets to lung (OD04451- 01)	5.8	11.9	6.1	8.5	10.7
Lung Margin (OD04451-02)	9.3	17.7	7.7	10.0	15.4
Normal Prostate	10.5	51.1	7.3	21.6	7.0

6546-1					
Prostate Cancer (OD04410)	12.2	14.9	14.9	9.0	17.4
Prostate Margin (OD04410)	14.6	13.8	25.3	19.2	29.7
Prostate Cancer (OD04720-01)	12.2	18.0	22.7	31.6	30.6
Prostate Margin (OD04720-02)	11.8	11.8	17.7	16.7	25.0
Normal Lung	7.3	17.8	17.6	12.8	22.4
Lung Met to Muscle (ODO4286)	12.7	27.4	25.0	31.0	22.1
Muscle Margin (ODO4286)	7.4	8.7	6.2	7.3	9.5
Lung Malignant Cancer (OD03126)	22.7	27.4	26.1	28.3	20.4
Lung Margin (OD03126)	12.7	21.9	21.9	13.9	31.9
Lung Cancer (OD04404)	17.9	41.5	41.5	30.4	48.0
Lung Margin (OD04404)	16.4	28.7	10.0	11.8	12.4
Lung Cancer (OD04565)	22.5	38.2	28.5	27.9	40.6
Lung Margin (OD04565)	8.1	11.7	8.5	8.6	16.3
Lung Cancer (OD04237-01)	9.8	7.1	10.9	8.8	9.6
Lung Margin (OD04237-02)	12.9	23.0	14.3	14.0	16.0
Ocular Mel Met to Liver (ODO4310)	0.6	0.5	0.7	0.5	1.1
Liver Margin (ODO4310)	3.5	2.6	1.8	3.3	3.0
Melanoma Metastasis	1.4	2.0	3.6	4.3	2.9
Lung Margin (OD04321)	20.4	14.4	25.2	24.0	18.6
Normal Kidney	20.2	19.9	18.0	17.4	26.1
Kidney Ca, Nuclear grade 2 (OD04338)	1.7	4.2	2.9	2.7	4.9
Kidney Margin	6.2	11.7	17.2	11.3	22.8

(OD04338)					
Kidney Ca Nuclear grade 1/2 (OD04339)	3.6	10.0	3.7	4.6	6.6
Kidney Margin (OD04339)	11.7	12.2	11.4	12.1	11.0
Kidney Ca, Clear cell type (OD04340)	46.7	50.7	66.0	65.1	70.7
Kidney Margin (OD04340)	15.3	19.1	14.8	12.9	16.8
Kidney Ca, Nuclear grade 3 (OD04348)	21.0	9.5	16.3	16.8	17.0
Kidney Margin (OD04348)	8.2	5.8	8.8	11.5	9.3
Kidney Cancer (OD04622-01)	24.0	25.3	27.7	24.8	41.5
Kidney Margin (OD04622-03)	2.1	4.6	3.4	3.1	5.9
Kidney Cancer (OD04450-01)	0.2	0.0	0.2	0.5	0.5
Kidney Margin (OD04450-03)	5.9	6.3	9.3	9.9	12.9
Kidney Cancer 8120607	7.3	9.1	11.9	12.8	13.4
Kidney Margin 8120608	12.2	6.2	7.9	5.6	8.0
Kidney Cancer 8120613	3.6	8.0	5.2	8.8	10.1
Kidney Margin 8120614	6.3	6.7	8.9	7.5	9.3
Kidney Cancer 9010320	18.7	61.1	25.0	21.9	22.1
Kidney Margin 9010321	14.0	20.3	16.4	12.9	17.9
Normal Uterus	4.1	5.6	3.3	8.4	6.0
Uterine Cancer 064011	9.6	10.7	17.1	11.7	15.6
Normal Thyroid	2.6	9.2	2.6	1.5	3.6
Thyroid Cancer	100.0	72.7	100.0	82.9	100.0
Thyroid Cancer A302152	7.6	4.5	12.5	8.0	11.7
Thyroid Margin A302153	3.0	2.4	2.8	3.2	6.0
Normal Breast	10.3	5.7	9.9	12.9	7.2

Breast Cancer	11.7	15.9	12.8	12.9	12.8
Breast Cancer (OD04590-01)	17.9	39.0	27.2	16.5	25.3
Breast Cancer Mets (OD04590-03)	26.1	66.0	35.4	42.0	27.9
Breast Cancer Metastasis	4.5	5.4	6.0	5.2	3.5
Breast Cancer	30.8	32.1	28.1	21.6	36.3
Breast Cancer	20.7	46.7	19.8	16.7	14.8
Breast Cancer 9100266	13.1	15.9	13.9	11.0	22.1
Breast Margin 9100265	10.4	14.4	15.6	16.4	20.9
Breast Cancer A209073	22.2	26.8	34.2	25.5	50.0
Breast Margin A2090734	6.7	9.7	7.1	4.3	11.3
Normal Liver	1.4	4.2	1.6	1.7	2.3
Liver Cancer	1.0	2.8	1.7	1.3	1.3
Liver Cancer 1025	1.4	1.1	3.3	2.3	3.2
Liver Cancer 1026	7.8	6.5	4.9	6.4	10.7
Liver Cancer 6004-T	5.0	9.9	4.2	3.0	5.2
Liver Tissue 6004-N	4.7	7.9	3.5	4.2	3.7
Liver Cancer 6005-T	7.9	11.5	8.2	10.3	6.7
Liver Tissue 6005-N	2.0	3.2	2.7	1.6	2.3
Normal Bladder	6.8	17.9	13.6	11.5	15.2
Bladder Cancer	10.7	22.8	14.5	14.2	14.2
Bladder Cancer	18.0	29.3	22.7	17.7	23.5
Bladder Cancer (OD04718-01)	14.5	29.3	26.1	21.0	28.3
Bladder Normal Adjacent (OD04718-03)	2.9	5.0	3.1	3.2	4.2
Normal Ovary	1.4	4.7	3.6	4.6	5.4
Ovarian Cancer	40.9	100.0	89.5	100.0	76.3
Ovarian Cancer (OD04768-07)	9.7	43.2	16.7	15.6	19.5
Ovary Margin	6.5	7.9	10.8	6.7	8.3

(OD04768-08)					
Normal Stomach	11.8	39.5	14.7	14.8	13.1
Gastric Cancer 9060358	1.4	6.0	2.9	2.8	2.9
Stomach Margin 9060359	6.4	19.9	7.4	10.8	8.7
Gastric Cancer 9060395	11.1	58.6	21.6	21.2	32.3
Stomach Margin 9060394	6.8	34.6	23.7	13.8	22.2
Gastric Cancer 9060397	15.4	78.5	24.8	25.2	31.9
Stomach Margin 9060396	3.9	14.5	6.1	7.5	7.9
Gastric Cancer 064005	2.5	14.8	7.0	7.3	13.0

Table 22. Panel 3D

Tissue Name	Rel. Exp.(%) Ag2263, Run 170189128	Tissue Name	Rel. Exp.(%) Ag2263, Run 170189128
Daoy- Medulloblastoma	19.1	Ca Ski- Cervical epidermoid carcinoma (metastasis)	0.4
TE671- Medulloblastoma	8.4	ES-2- Ovarian clear cell carcinoma	0.0
D283 Med- Medulloblastoma	39.2	Ramos- Stimulated with PMA/ionomycin 6h	0.0
PFSK-1- Primitive Neuroectodermal	59.5	Ramos- Stimulated with PMA/ionomycin 14h	0.0
XF-498- CNS	0.9	MEG-01- Chronic myelogenous leukemia (megokaryoblast)	3.8
SNB-78- Glioma	35.4	Raji- Burkitt's lymphoma	0.0
SF-268- Glioblastoma	0.0	Daudi- Burkitt's lymphoma	0.0
T98G- Glioblastoma	1.2	U266- B-cell plasmacytoma	0.0
SK-N-SH- Neuroblastoma (metastasis)	94.6	CA46- Burkitt's lymphoma	0.0
SF-295- Glioblastoma	0.3	RL- non-Hodgkin's B-cell lymphoma	0.0
Cerebellum	37.4	JM1- pre-B-cell lymphoma	0.0
Cerebellum	35.1	Jurkat- T cell leukemia	0.5
NCI-H292- Mucoepidermoid lung carcinoma	4.3	TF-1- Erythroleukemia	73.2
DMS-114- Small cell	6.6	HUT 78- T-cell lymphoma	0.0

lung cancer			
DMS-79- Small cell lung cancer	100.0	U937- Histiocytic lymphoma	0.0
NCI-H146- Small cell lung cancer	37.4	KU-812- Myelogenous leukemia	0.6
NCI-H526- Small cell lung cancer	17.2	769-P- Clear cell renal carcinoma	0.0
NCI-N417- Small cell lung cancer	88.9	Caki-2- Clear cell renal carcinoma	0.0
NCI-H82- Small cell lung cancer	95.3	SW 839- Clear cell renal carcinoma	0.0
NCI-H157- Squamous cell lung cancer (metastasis)	0.8	G401- Wilms' tumor	2.8
NCI-H1155- Large cell lung cancer	55.5	Hs766T- Pancreatic carcinoma (LN metastasis)	0.6
NCI-H1299- Large cell lung cancer	0.0	CAPAN-1- Pancreatic adenocarcinoma (liver metastasis)	3.1
NCI-H727- Lung carcinoid	0.7	SU86.86- Pancreatic carcinoma (liver metastasis)	0.4
NCI-UMC-11- Lung carcinoid	7.9	BxPC-3- Pancreatic adenocarcinoma	22.8
LX-1- Small cell lung cancer	1.8	HPAC- Pancreatic adenocarcinoma	35.6
Colo-205- Colon cancer	0.3	MIA PaCa-2- Pancreatic carcinoma	0.6
KM12- Colon cancer	0.1	CFPAC-1- Pancreatic ductal adenocarcinoma	1.1
KM20L2- Colon cancer	0.6	PANC-1- Pancreatic epithelioid ductal carcinoma	0.3
NCI-H716- Colon cancer	70.2	T24- Bladder carcinma (transitional cell)	0.0
SW-48- Colon adenocarcinoma	0.0	5637- Bladder carcinoma	2.2
SW1116- Colon adenocarcinoma	16.6	HT-1197- Bladder carcinoma	0.4
LS 174T- Colon adenocarcinoma	4.2	UM-UC-3- Bladder carcinma (transitional cell)	0.2
SW-948- Colon adenocarcinoma	0.4	A204- Rhabdomyosarcoma	0.0
SW-480- Colon adenocarcinoma	0.0	HT-1080- Fibrosarcoma	7.9
NCI-SNU-5- Gastric carcinoma	1.7	MG-63- Osteosarcoma	16.3
KATO III- Gastric	17.4	SK-LMS-1- Leiomyosarcoma	0.0

carcinoma		(vulva)	
NCI-SNU-16- Gastric carcinoma	0.7	SJRH30- Rhabdomyosarcoma (met to bone marrow)	3.9
NCI-SNU-1- Gastric carcinoma	23.0	A431- Epidermoid carcinoma	34.9
RF-1- Gastric adenocarcinoma	0.0	WM266-4- Melanoma	0.0
RF-48- Gastric adenocarcinoma	0.0	DU 145- Prostate carcinoma (brain metastasis)	0.0
MKN-45- Gastric carcinoma	11.5	MDA-MB-468- Breast adenocarcinoma	16.4
NCI-N87- Gastric carcinoma	24.0	SCC-4- Squamous cell carcinoma of tongue	0.0
OVCAR-5- Ovarian carcinoma	3.7	SCC-9- Squamous cell carcinoma of tongue	0.0
RL95-2- Uterine carcinoma	4.6	SCC-15- Squamous cell carcinoma of tongue	0.0
HelaS3- Cervical adenocarcinoma	5.9	CAL 27- Squamous cell carcinoma of tongue	7.1

Table 23. Panel 4D

Tissue Name	Rel. Exp.(%) Ag1522, Run 145789191	Rel. Exp.(%) Ag1848, Run 160202841	Rel. Exp.(%) Ag2263, Run 151562852	Rel. Exp.(%) Ag2422, Run 159318890
Secondary Th1 act	0.0	0.1	0.0	0.2
Secondary Th2 act	0.0	0.0	0.0	0.0
Secondary Tr1 act	0.0	0.0	0.0	4.6
Secondary Th1 rest	0.1	0.0	0.1	0.0
Secondary Th2 rest	0.0	0.0	0.0	0.0
Secondary Tr1 rest	0.0	0.0	0.0	0.2
Primary Th1 act	0.1	0.2	0.2	1.0
Primary Th2 act	0.1	0.2	0.1	0.3
Primary Tr1 act	0.2	0.5	0.0	0.6
Primary Th1 rest	0.0	0.0	0.0	0.0
Primary Th2 rest	0.0	0.0	0.0	0.0
Primary Tr1 rest	0.0	0.0	0.0	0.0
CD45RA CD4 lymphocyte act	4.9	6.3	8.5	10.6
CD45RO CD4 lymphocyte act	0.0	0.0	0.0	0.0
CD8 lymphocyte act	0.0	0.0	0.0	0.0
Secondary CD8 lymphocyte rest	0.0	0.0	0.0	0.0
Secondary CD8 lymphocyte act	0.0	0.0	0.0	0.0

CD4 lymphocyte none	0.0	0.0	0.0	0.0
2ry Th1/Th2/Tr1_anti-CD95 CH11	0.0	0.0	0.0	0.0
LAK cells rest	1.8	2.7	2.0	5.8
LAK cells IL-2	0.0	0.0	0.0	0.0
LAK cells IL-2+IL-12	0.0	0.1	0.0	0.2
LAK cells IL-2+IFN gamma	0.0	0.1	0.0	0.2
LAK cells IL-2+ IL-18	0.0	0.4	0.0	0.1
LAK cells PMA/ionomycin	1.1	1.0	1.7	2.5
NK Cells IL-2 rest	0.0	0.1	0.0	0.0
Two Way MLR 3 day	0.0	0.1	0.2	0.2
Two Way MLR 5 day	0.2	0.3	0.8	0.6
Two Way MLR 7 day	0.5	0.2	0.1	0.3
PBMC rest	0.0	0.0	0.1	0.0
PBMC PWM	0.0	0.1	0.0	0.0
PBMC PHA-L	0.0	0.1	0.0	0.0
Ramos (B cell) none	0.0	0.0	0.0	0.0
Ramos (B cell) ionomycin	0.0	0.0	0.0	0.0
B lymphocytes PWM	0.2	0.0	0.0	0.0
B lymphocytes CD40L and IL-4	0.0	0.1	0.1	0.3
EOL-1 dbcAMP	0.2	0.2	0.4	0.0
EOL-1 dbcAMP PMA/ionomycin	0.1	0.4	0.2	0.6
Dendritic cells none	1.4	1.1	1.0	2.8
Dendritic cells LPS	0.3	0.4	0.3	0.4
Dendritic cells anti-CD40	2.4	3.0	3.5	6.7
Monocytes rest	0.8	0.8	0.6	1.3
Monocytes LPS	0.0	0.0	0.3	0.0
Macrophages rest	1.3	1.0	0.0	2.0
Macrophages LPS	0.0	0.2	0.1	0.4
HUVEC none	1.1	1.4	0.6	2.5
HUVEC starved	4.4	4.7	2.9	6.0
HUVEC IL-1beta	1.7	2.8	1.0	2.3
HUVEC IFN gamma	1.6	1.4	2.5	1.9
HUVEC TNF alpha + IFN gamma	0.3	0.3	0.5	0.5
HUVEC TNF alpha + IL4	0.2	0.3	0.3	1.3
HUVEC IL-11	0.9	1.2	2.2	0.5

Lung Microvascular EC none	2.2	6.5	2.8	6.7
Lung Microvascular EC TNFalpha + IL-1beta	12.7	11.9	8.5	15.5
Microvascular Dermal EC none	32.1	30.8	22.4	22.4
Microvascular Dermal EC TNFalpha + IL-1beta	16.3	16.2	8.8	14.4
Bronchial epithelium TNFalpha + IL1beta	24.0	31.2	15.1	50.7
Small airway epithelium none	8.8	5.9	6.7	12.8
Small airway epithelium TNFalpha + IL-1beta	31.9	43.5	21.0	44.8
Coronary artery SMC rest	27.4	28.7	8.5	35.8
Coronary artery SMC TNFalpha + IL-1beta	12.9	21.6	27.4	17.8
Astrocytes rest	17.1	14.9	23.8	24.3
Astrocytes TNFalpha + IL-1beta	32.8	29.5	28.1	35.1
KU-812 (Basophil) rest	1.0	1.8	1.3	0.7
KU-812 (Basophil) PMA/ionomycin	1.4	3.3	2.0	3.7
CCD1106 (Keratinocytes) none	1.4	0.2	0.7	2.7
CCD1106 (Keratinocytes) TNFalpha + IL-1beta	0.9	0.3	0.8	1.3
Liver cirrhosis	2.9	3.0	2.4	4.8
Lupus kidney	3.0	2.9	0.9	4.4
NCI-H292 none	10.4	13.7	5.6	18.8
NCI-H292 IL-4	14.2	14.9	6.8	17.1
NCI-H292 IL-9	13.2	16.7	9.3	12.8
NCI-H292 IL-13	9.4	8.6	15.9	9.0
NCI-H292 IFN gamma	3.8	4.7	4.7	5.3
HPAEC none	1.2	1.0	1.6	2.8
HPAEC TNF alpha + IL-1 beta	5.8	2.6	4.7	6.0
Lung fibroblast none	100.0	100.0	100.0	100.0
Lung fibroblast TNF alpha + IL-1 beta	8.5	12.2	15.9	15.2
Lung fibroblast IL-4	74.2	79.6	45.7	97.3
Lung fibroblast IL-9	27.7	48.6	30.6	50.3

Lung fibroblast IL-13	48.0	39.5	27.4	55.9
Lung fibroblast IFN gamma	76.3	82.9	42.6	98.6
Dermal fibroblast CCD1070 rest	52.9	56.3	27.2	65.5
Dermal fibroblast CCD1070 TNF alpha	33.9	42.6	19.8	46.7
Dermal fibroblast CCD1070 IL-1 beta	29.1	27.9	70.2	28.9
Dermal fibroblast IFN gamma	6.1	3.6	8.9	7.9
Dermal fibroblast IL-4	14.5	16.2	17.3	18.9
IBD Colitis 2	0.1	0.1	0.2	0.5
IBD Crohn's	0.6	0.4	0.0	0.8
Colon	7.6	6.4	8.0	11.3
Lung	59.5	75.8	47.6	74.7
Thymus	16.5	17.3	10.2	19.6
Kidney	6.8	9.0	3.0	6.5

Table 24. Panel CNS_1

Tissue Name	Rel. Exp.(%) Ag2263, Run 171669090	Tissue Name	Rel. Exp.(%) Ag2263, Run 171669090
BA4 Control	22.8	BA17 PSP	11.2
BA4 Control2	38.2	BA17 PSP2	7.1
BA4 Alzheimer's2	3.7	Sub Nigra Control	100.0
BA4 Parkinson's	45.7	Sub Nigra Control2	51.8
BA4 Parkinson's2	31.2	Sub Nigra Alzheimer's2	30.8
BA4 Huntington's	12.3	Sub Nigra Parkinson's2	89.5
BA4 Huntington's2	12.2	Sub Nigra Huntington's	59.0
BA4 PSP	13.6	Sub Nigra Huntington's2	16.2
BA4 PSP2	42.6	Sub Nigra PSP2	22.5
BA4 Depression	27.9	Sub Nigra Depression	40.6
BA4 Depression2	10.9	Sub Nigra Depression2	12.8
BA7 Control	28.3	Glob Palladus Control	36.1
BA7 Control2	27.2	Glob Palladus Control2	21.3
BA7	5.5	Glob Palladus	26.1

Alzheimer's2		Alzheimer's	
BA7 Parkinson's	13.2	Glob Palladus Alzheimer's2	11.2
BA7 Parkinson's2	12.8	Glob Palladus Parkinson's	73.2
BA7 Huntington's	14.8	Glob Palladus Parkinson's2	15.7
BA7 Huntington's2	22.2	Glob Palladus PSP	15.0
BA7 PSP	29.1	Glob Palladus PSP2	10.4
BA7 PSP2	8.9	Glob Palladus Depression	28.3
BA7 Depression	5.4	Temp Pole Control	5.4
BA9 Control	14.3	Temp Pole Control2	25.2
BA9 Control2	57.0	Temp Pole Alzheimer's	10.0
BA9 Alzheimer's	5.5	Temp Pole Alzheimer's2	2.5
BA9 Alzheimer's2	13.8	Temp Pole Parkinson's	15.5
BA9 Parkinson's	16.2	Temp Pole Parkinson's2	27.9
BA9 Parkinson's2	21.0	Temp Pole Huntington's	22.4
BA9 Huntington's	21.5	Temp Pole PSP	1.3
BA9 Huntington's2	11.9	Temp Pole PSP2	6.4
BA9 PSP	27.7	Temp Pole Depression2	12.3
BA9 PSP2	5.9	Cing Gyr Control	48.3
BA9 Depression	11.0	Cing Gyr Control2	28.1
BA9 Depression2	9.5	Cing Gyr Alzheimer's	27.2
BA17 Control	25.0	Cing Gyr Alzheimer's2	13.1
BA17 Control2	45.7	Cing Gyr Parkinson's	29.7
BA17 Alzheimer's2	6.5	Cing Gyr Parkinson's2	37.4
BA17 Parkinson's	35.4	Cing Gyr Huntington's	70.7
BA17 Parkinson's2	15.3	Cing Gyr Huntington's2	32.1
BA17 Huntington's	15.5	Cing Gyr PSP	42.6

BA17 Huntington's2	8.1	Cing Gyr PSP2	8.3
BA17 Depression	26.2	Cing Gyr Depression	20.6
BA17 Depression2	59.9	Cing Gyr Depression2	36.3

CNS_neurodegeneration_v1.0 Summary: Ag1848/Ag2263/Ag2422

Multiple experiments using different probe/primer sets produce results that are in good agreement. Highest expression of a NOV1 gene is detected in the occipital cortex of a control patient. Significant levels of expression are also detected in the hippocampus, inferior temporal cortex, and the superior temporal cortex of brain tissue from an Alzheimer's patient.

Based on its homology, a NOV1 gene product is most similar to an UNC5H receptor, which as a class is known to act both in axon guidance and neuronal migration during development, as well as in inducing apoptosis (except when stimulated by the ligand netrin-1). Panel CNS_Neurodegeneration_V1.0 shows a moderate increase (1.5 to 2-fold) in the temporal cortex of the Alzheimer's disease brain when compared to non-demented elderly either with or without a high amyloid plaque load [this difference is apparent after scaling the RTQ-PCR data based upon overall RNA amount/quality, and is most apparent on Aq2263]. Thus NOV1 gene represents a protein that differentiates demented and non-demented elderly who have a severe amyloid plaque load, making it an excellent drug target in Alzheimer's disease. The modulation and/or selective stimulation of this receptor may be of use in enhancing or directing compensatory synatogenesis and axon/dendritic outgrowth in response to neuronal death (stroke, head trauma) neurodegeneration (Alzheimer's, Parkinson's, Huntington's, spinocerebellar ataxia, progressive supranuclear palsy) or spinal cord injury. Furthermore, antagonism of this receptor may decrease apoptosis in Alzheimer's disease.

References:

- Ellezam B, Selles-Navarro I, Manitt C, Kennedy TE, McKerracher L. Expression of netrin-1 and its receptors DCC and UNC-5H2 after axotomy and during regeneration of adult rat retinal ganglion cells. Exp Neurol 2001 Mar;168(1):105-15
- Netrins are a family of chemotropic factors that guide axon outgrowth during development; however, their function in the adult CNS remains to be established. We examined the expression of the netrin receptors DCC and UNC5H2 in adult rat retinal ganglion cells (RGCs) after grafting a peripheral nerve (PN) to the transected optic nerve and

following optic nerve transection alone. In situ hybridization revealed that both Dcc and Unc5h2 mRNAs are expressed by normal adult RGCs. In addition, netrin-1 was found to be constitutively expressed by RGCs. Quantitative analysis using in situ hybridization demonstrated that both Dcc and Unc5h2 were down-regulated by RGCs following axotomy. In the presence of an attached PN graft, Dcc and Unc5h2 were similarly down-regulated in surviving RGCs regardless of their success in regenerating an axon. Northern blot analysis demonstrated expression of netrin-1 in both optic and sciatic nerve, and Western blot analysis revealed the presence of netrin protein in both nerves. Immunohistochemical analysis indicated that netrin protein was closely associated with glial cells in the optic nerve. These results suggest that netrin-1, DCC, and UNC5H2 may contribute to regulating the regenerative capacity of adult RGCs.

2. Braisted JE, Catalano SM, Stimac R, Kennedy TE, Tessier-Lavigne M, Shatz CJ, O'Leary DD Netrin-1 promotes thalamic axon growth and is required for proper development of the thalamocortical projection. *J Neurosci* 2000 Aug 1;20(15):5792-801

The thalamocortical axon (TCA) projection originates in dorsal thalamus, conveys sensory input to the neocortex, and has a critical role in cortical development. We show that the secreted axon guidance molecule netrin-1 acts in vitro as an attractant and growth promoter for dorsal thalamic axons and is required for the proper development of the TCA projection in vivo. As TCAs approach the hypothalamus, they turn laterally into the ventral telencephalon and extend toward the cortex through a population of netrin-1-expressing cells. DCC and neogenin, receptors implicated in mediating the attractant effects of netrin-1, are expressed in dorsal thalamus, whereas unc5h2 and unc5h3, netrin-1 receptors implicated in repulsion, are not. In vitro, dorsal thalamic axons show biased growth toward a source of netrin-1, which can be abolished by netrin-1-blocking antibodies. Netrin-1 also enhances overall axon outgrowth from explants of dorsal thalamus. The biased growth of dorsal thalamic axons toward the internal capsule zone of ventral telencephalic explants is attenuated, but not significantly, by netrin-1-blocking antibodies, suggesting that it releases another attractant activity for TCAs in addition to netrin-1. Analyses of netrin-1 $-/-$ mice reveal that the TCA projection through the ventral telencephalon is disorganized, their pathway is abnormally restricted, and fewer dorsal thalamic axons reach cortex. These findings demonstrate that netrin-1 promotes the growth of TCAs through the ventral telencephalon and cooperates with other guidance cues to control their pathfinding from dorsal thalamus to cortex.

Panel 1.2 Summary: Ag1522

Expression of a NOV1 gene is highest in CNS cancer cell lines (CT=26.1). Of nine tissue samples derived from CNS cancer cell lines, expression of a NOV1 gene occurs in all samples, with expression high in three samples, moderate in five samples and low in one sample. High expression is also detectable in melanoma cell lines. Significant expression of a NOV1 gene is seen in gastric cancer and all ten samples of lung cancer cell lines in this sample. Thus, expression of a NOV1 gene could be used to distinguish those cancer cell lines from normal tissues. In addition, therapeutic modulation of the expression, or activity of a NOV1 gene product, might be of use in the treatment of melanoma, gastric cancer, lung cancer and brain cancer.

10 **Panel 1.3D Summary: Ag1522/Ag1848/Ag2263/Ag2422**

Four experiments using different probe/primer sets on the same tissue panel produce results that are in excellent agreement. In all four experiments, highest expression of a NOV1 gene is detected in CNS cancer cell lines. Expression is also significant in lung cancer and melanoma cell lines and in healthy brain tissue from the hippocampus and thalamus regions. Thus, the expression of a NOV1 gene could be used to distinguish these tissue samples from other samples. Moreover, therapeutic modulation of the expression, or function, of the CG50126-01 gene, through the use of small molecule drugs or antibodies, might be beneficial in the treatment of melanoma, lung cancer and brain cancer.

Among metabolic tissues, there is high expression of a NOV1 gene in adult heart tissue (CT=27.8) and moderate expression in fetal heart, adult and fetal liver, pancreas, adrenal gland, thyroid and pituitary. This widespread expression of a NOV1 gene product in tissues with metabolic function suggests a possible role for a NOV1 gene product in metabolic disorders, including obesity and diabetes.

The UNC5H receptors act both in axon guidance and neuronal migration during development, as well as inducers of apoptosis (except when stimulated by the ligand netrin-1). This panel shows widespread expression of a NOV1 gene in the central nervous system. Please see CNS_neurodegeneration_v1.0 for discussion of potential utility in the central nervous system.

30 **Panel 2D Summary: Ag1522/Ag1848/Ag2263/Ag2422**

Results from multiple experiments with four different probe and primer sets are in very good agreement. In all four experiments, highest expression of a NOV1 gene is detected in thyroid and ovarian cancers (CTs = 27-30), with lower expression also seen in most of the other tissues on this panel. Thus, the expression of a NOV1 gene could be used to distinguish

ovarian and thyroid cancer cell lines from other tissues. Moreover, therapeutic modulation of the expression this gene, or its function, through the use of small molecule drugs or antibodies, might be of benefit in the treatment of ovarian and thyroid cancer. In addition, experiments with the probe and primer set Ag2263 show differential expression between samples derived from lung cancer and their adjacent normal tissues. Thus, expression of a NOV1 gene could be used to distinguish cancerous lung tissue from normal lung tissue. Moreover, therapeutic modulation of the expression or function of this gene or its protein product, through the use of antibodies or small molecule drugs, might be of benefit in the treatment of lung cancer.

Panel 3D Summary: Ag2263

Expression of a NOV1 gene occurs at moderate levels across all the tissues in this panel. Highest expression is detected in a small cell lung cancer (CT = 30.6) and neuroblastoma (CT = 30.7). In addition, significant expression is detected in a cluster of small cell lung cancer lines. Thus, this gene could be used to distinguish lung cancer cell lines from other samples. Moreover, therapeutic modulation of the CG50126-01 gene or its protein product, through the use of small molecule drugs or antibodies might be of benefit in the treatment of small cell lung cancer.

Panel 4D Summary: Ag1522/Ag1848/Ag2263/Ag2422

Experiments using each of the four probe and primer sets that correspond to a NOV1 gene produce results that are in excellent agreement. In all the experiments, expression of a NOV1 gene occurs at moderate to low levels in many of the tissues in the sample. Highest expression in each experiment occurs in lung fibroblasts (CT = 29). Moderate expression in lung fibroblasts treated with IL-4 is also consistent among all four experiments (CT = 30). Lower expression is also detected in a variety of fibroblasts, endothelial and smooth muscle cells. The expression of a NOV1 gene produces a complex profile; it is upregulated by TNF-alpha in small airway epithelium, but clearly downregulated by the same stimulus in lung fibroblasts. The gene most probably encodes a netrin receptor that may be important in understanding cell migration. Regulation of the protein encoded for by a NOV1 gene could potentially control the progression of keloid formation, emphysema and other conditions in which TNF-alpha and IL-1 beta are present and tissue remodeling may occur.

Panel CNS_1 Summary: Ag2263

Expression of NOV1 is moderate to low across many of the tissues in this panel. Highest expression is detected in the substantia nigra (CT = 31.4). Although no disease-specific expression is seen in this panel, the expression profile confirms the expression of this

gene in the central nervous system. Please see CNS_neurodegeneration_v1.0 for potential utility of the CG50126-01 gene regarding the CNS.

NOV2

5 Expression of gene CG50718-01 was assessed using the primer-probe sets Ag1555 and Ag2315, described in Tables 25 and 26. Results of the RTQ-PCR runs are shown in Tables 27, 28, 29 and 30.

Table 25. Probe Name Ag1555

Primers	Sequences	Length	Start Position	SEQ ID NO:
Forward	5'-gaagtgaagaatgtgcatggt-3'	22	6680	145
Probe	TET-5'-caccagtgcattctggatctcttatca-3'-TAMRA	27	6730	146
Reverse	5'-tgggctgattacttccttatt-3'	22	6757	147

Table 26. Probe Name Ag2315

Primers	Sequences	Length	Start Position	SEQ ID NO:
Forward	5'-agatgagtcagtgccgtagc-3'	21	3711	148
Probe	TET-5'-cctccacaaaatttgactttaactg-3'-TAMRA	29	3733	149
Reverse	5'-tccatttcagccatacaaagtc-3'	22	3769	150

Table 27. Panel 1.3D

Tissue Name	Rel. Exp.(%) Ag1555, Run 146380268	Rel. Exp.(%) Ag1555, Run 147775028	Rel. Exp.(%) Ag2315, Run 159198312	Tissue Name	Rel. Exp.(%) Ag1555, Run 146380268	Rel. Exp.(%) Ag1555, Run 147775028	Rel. Exp.(%) Ag2315, Run 159198312
Liver adenocarcinoma	0.0	0.0	0.0	Kidney (fetal)	33.9	37.6	90.8
Pancreas	5.8	1.6	3.9	Renal ca. 786-0	0.0	0.0	0.0
Pancreatic ca. CAPAN 2	0.0	0.0	0.0	Renal ca. A498	0.0	0.0	0.0
Adrenal gland	0.0	1.9	0.0	Renal ca. RXF 393	0.0	0.0	0.0
Thyroid	8.3	24.7	25.3	Renal ca. ACHN	0.0	0.0	0.0
Salivary gland	1.0	0.0	0.0	Renal ca. UO-31	0.0	1.4	0.0
Pituitary gland	0.0	0.0	8.0	Renal ca. TK-10	0.0	0.0	0.0
Brain (fetal)	0.6	0.0	3.8	Liver	0.0	0.0	0.0
Brain (whole)	1.3	1.6	3.3	Liver (fetal)	0.0	3.6	0.0

Brain (amygdala)	3.4	4.0	6.7	Liver ca. (hepatoblast) HepG2	0.0	0.0	0.0
Brain (cerebellum)	0.0	0.0	0.0	Lung	51.1	52.5	70.7
Brain (hippocampus)	1.2	0.6	5.9	Lung (fetal)	100.0	100.0	74.2
Brain (substantia nigra)	0.0	0.0	0.0	Lung ca. (small cell) LX-1	0.0	0.0	0.0
Brain (thalamus)	3.2	1.3	4.0	Lung ca. (small cell) NCI-H69	2.4	0.0	32.5
Cerebral Cortex	0.0	0.0	12.4	Lung ca. (s. cell var.) SHP-77	0.0	0.0	10.7
Spinal cord	1.1	0.0	0.0	Lung ca. (large cell) NCI-H460	0.0	0.0	0.0
glio/astro U87-MG	0.0	2.7	0.0	Lung ca. (non-sm. cell) A549	0.0	0.0	0.0
glio/astro U-118-MG	27.2	34.6	15.8	Lung ca. (non-s. cell) NCI-H23	0.0	0.0	0.0
astrocytoma SW1783	5.4	13.8	16.0	Lung ca. (non-s. cell) HOP-62	0.7	0.9	0.0
neuro*; met SK-N-AS	0.0	0.6	0.0	Lung ca. (non-s. cl) NCI-H522	9.9	5.4	20.9
astrocytoma SF-539	0.8	0.0	0.0	Lung ca. (squam.) SW 900	0.0	0.0	0.0
astrocytoma SNB-75	0.0	0.0	0.0	Lung ca. (squam.) NCI-H596	1.3	2.2	9.0
glioma SNB-19	0.0	0.0	0.0	Mammary gland	13.0	26.6	11.5
glioma U251	0.0	0.0	0.0	Breast ca.* (pl.ef) MCF-7	3.9	0.9	15.6
glioma SF-295	1.3	3.3	0.0	Breast ca.* (pl.ef) MDA-MB-231	0.0	0.0	0.0
Heart (Fetal)	0.0	0.0	7.4	Breast ca.* (pl. ef) T47D	0.0	0.0	6.1
Heart	0.0	5.7	0.0	Breast ca. BT-549	0.0	0.0	0.0

Skeletal muscle (Fetal)	3.5	1.6	15.1	Breast ca. MDA-N	0.0	0.0	0.0
Skeletal muscle	0.0	1.4	2.5	Ovary	5.2	1.6	5.8
Bone marrow	1.0	4.1	0.0	Ovarian ca. OVCAR-3	0.0	0.0	6.7
Thymus	1.0	0.0	8.8	Ovarian ca. OVCAR-4	0.0	0.0	0.0
Spleen	0.0	0.0	0.0	Ovarian ca. OVCAR-5	0.0	0.0	0.0
Lymph node	3.7	4.8	7.1	Ovarian ca. OVCAR-8	0.0	0.0	0.0
Colorectal	0.0	0.0	0.0	Ovarian ca. IGROV-1	0.0	0.0	0.0
Stomach	1.2	2.3	0.0	Ovarian ca. (ascites) SK-OV-3	0.0	0.0	0.0
Small intestine	2.2	6.7	0.0	Uterus	0.0	0.9	0.0
Colon ca. SW480	0.0	0.0	0.0	Placenta	11.8	27.7	23.7
Colon ca.* SW620 (SW480 met)	0.0	0.0	0.0	Prostate	3.5	0.9	3.0
Colon ca. HT29	0.0	0.0	0.0	Prostate ca.* (bone met) PC-3	0.0	0.0	0.0
Colon ca. HCT-116	0.0	0.0	2.7	Testis	58.2	67.4	21.5
Colon ca. CaCo-2	0.0	0.0	0.0	Melanoma Hs688(A).T	22.7	52.1	18.2
CC Well to Mod Diff (ODO3866)	0.0	0.0	0.0	Melanoma* (met) Hs688(B).T	4.8	4.2	0.0
Colon ca. HCC-2998	0.0	0.0	0.0	Melanoma UACC-62	0.0	1.5	0.0
Gastric ca. (liver met) NCI-N87	0.0	0.0	0.0	Melanoma M14	0.0	0.0	0.0
Bladder	2.0	0.0	6.1	Melanoma LOX IMVI	0.0	0.0	0.0
Trachea	2.4	3.6	0.0	Melanoma* (met) SK-MEL-5	0.0	0.0	0.0
Kidney	15.5	17.8	22.2	Adipose	38.2	40.6	100.0

Table 28. Panel 2D

Tissue Name	Rel. Exp.(%) Ag1555, Run 147775063	Rel. Exp.(%) Ag1555, Run 159601974	Rel. Exp.(%) Ag2315, Run 159200827	Tissue Name	Rel. Exp.(%) Ag1555, Run 147775063	Rel. Exp.(%) Ag1555, Run 159601974	Rel. Exp.(%) Ag2315, Run 159200827
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Normal Colon	3.8	7.1	12.4	Kidney Margin 8120608	2.9	1.2	1.7
CC Well to Mod Diff (ODO3866)	1.0	0.0	2.3	Kidney Cancer 8120613	0.0	0.0	0.0
CC Margin (ODO3866)	0.0	0.0	0.7	Kidney Margin 8120614	1.2	2.6	1.8
CC Gr.2 rectosigmoid (ODO3868)	0.0	0.0	0.0	Kidney Cancer 9010320	2.7	2.6	2.1
CC Margin (ODO3868)	0.0	0.7	0.0	Kidney Margin 9010321	6.6	5.9	4.9
CC Mod Diff (ODO3920)	0.0	0.0	0.0	Normal Uterus	0.0	0.0	1.8
CC Margin (ODO3920)	0.0	0.0	2.2	Uterine Cancer 064011	0.0	0.0	4.5
CC Gr.2 ascend colon (ODO3921)	0.0	0.0	0.0	Normal Thyroid	34.9	27.4	11.4
CC Margin (ODO3921)	0.0	0.0	0.0	Thyroid Cancer	2.9	7.2	7.9
CC from Partial Hepatectomy (ODO4309) Mets	1.6	1.1	0.0	Thyroid Cancer A302152	1.3	3.3	2.0
Liver Margin (ODO4309)	0.0	0.0	2.0	Thyroid Margin A302153	49.7	69.7	72.2
Colon mets to lung (OD04451-01)	2.0	1.0	0.5	Normal Breast	10.0	8.9	25.3
Lung Margin (OD04451-02)	8.6	10.0	10.9	Breast Cancer	10.2	3.0	1.1
Normal Prostate 6546-1	4.2	12.2	1.4	Breast Cancer (OD04590-01)	0.0	2.8	3.9
Prostate Cancer (OD04410)	0.0	0.0	3.4	Breast Cancer Mets (OD04590-03)	7.8	7.3	7.9
Prostate Margin (OD04410)	0.8	6.4	2.2	Breast Cancer Metastasis	4.1	8.0	3.5

Prostate Cancer (OD04720-01)	9.5	11.7	19.6	Breast Cancer	0.0	0.0	1.2
Prostate Margin (OD04720-02)	10.0	11.3	24.5	Breast Cancer	3.7	2.9	0.9
Normal Lung	59.9	61.1	87.7	Breast Cancer 9100266	2.2	1.1	1.5
Lung Met to Muscle (ODO4286)	0.0	0.0	0.0	Breast Margin 9100265	0.0	0.0	0.5
Muscle Margin (ODO4286)	0.9	0.0	1.8	Breast Cancer A209073	0.7	1.1	1.9
Lung Malignant Cancer (OD03126)	1.9	2.8	1.7	Breast Margin A2090734	0.0	1.2	0.9
Lung Margin (OD03126)	36.3	35.6	43.8	Normal Liver	0.0	0.0	0.0
Lung Cancer (OD04404)	2.2	4.4	4.3	Liver Cancer	0.0	0.0	0.6
Lung Margin (OD04404)	9.5	4.2	8.4	Liver Cancer 1025	0.0	0.0	0.0
Lung Cancer (OD04565)	0.0	0.0	0.0	Liver Cancer 1026	0.0	0.0	0.0
Lung Margin (OD04565)	10.8	9.7	14.1	Liver Cancer 6004-T	0.0	1.0	0.6
Lung Cancer (OD04237-01)	0.0	0.0	0.0	Liver Tissue 6004-N	0.0	0.0	0.0
Lung Margin (OD04237-02)	30.1	18.4	29.3	Liver Cancer 6005-T	0.0	0.0	0.0
Ocular Mel Met to Liver (ODO4310)	0.0	0.0	0.6	Liver Tissue 6005-N	0.0	0.0	0.0
Liver Margin (ODO4310)	1.0	2.0	0.0	Normal Bladder	4.7	2.2	2.9
Melanoma Metastasis	0.0	0.0	0.0	Bladder Cancer	0.0	0.0	0.0
Lung Margin (OD04321)	25.7	47.0	49.0	Bladder Cancer	0.0	4.2	5.5
Normal Kidney	86.5	100.0	100.0	Bladder Cancer (OD04718-	0.7	1.6	1.1

				01)			
Kidney Ca, Nuclear grade 2 (OD04338)	2.2	0.0	1.1	Bladder Normal Adjacent (OD04718- 03)	4.4	0.9	6.3
Kidney Margin (OD04338)	55.1	35.8	58.2	Normal Ovary	1.7	0.0	0.9
Kidney Ca Nuclear grade 1/2 (OD04339)	0.0	0.0	0.0	Ovarian Cancer	0.0	4.2	3.3
Kidney Margin (OD04339)	77.9	63.7	77.9	Ovarian Cancer (OD04768- 07)	0.0	0.0	0.0
Kidney Ca, Clear cell type (OD04340)	1.7	0.0	0.0	Ovary Margin (OD04768- 08)	9.4	5.5	6.9
Kidney Margin (OD04340)	100.0	53.2	62.4	Normal Stomach	0.0	0.0	0.0
Kidney Ca, Nuclear grade 3 (OD04348)	25.9	23.2	0.0	Gastric Cancer 9060358	0.0	0.0	1.5
Kidney Margin (OD04348)	40.9	50.3	54.7	Stomach Margin 9060359	0.0	0.0	2.0
Kidney Cancer (OD04622- 01)	0.6	0.0	0.0	Gastric Cancer 9060395	0.9	1.2	1.8
Kidney Margin (OD04622- 03)	0.0	0.0	1.4	Stomach Margin 9060394	0.0	1.0	0.7
Kidney Cancer (OD04450- 01)	0.0	0.0	0.0	Gastric Cancer 9060397	0.0	0.0	0.0
Kidney Margin (OD04450- 03)	40.3	51.1	50.7	Stomach Margin 9060396	0.0	0.0	0.0
Kidney Cancer 8120607	0.0	0.0	0.0	Gastric Cancer 064005	0.0	0.0	2.5

Table 29. Panel 4D

Tissue Name	Rel. Exp.(%)	Rel. Exp.(%)	Tissue Name	Rel. Exp.(%)	Rel. Exp.(%)
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	Ag1555, Run 147775116	Ag2315, Run 159202089		Ag1555, Run 147775116	Ag2315, Run 159202089
Secondary Th1 act	0.0	0.0	HUVEC IL-1beta	0.0	0.0
Secondary Th2 act	0.0	0.0	HUVEC IFN gamma	0.0	0.0
Secondary Tr1 act	0.0	0.7	HUVEC TNF alpha + IFN gamma	0.0	0.0
Secondary Th1 rest	0.0	0.0	HUVEC TNF alpha + IL4	0.0	0.0
Secondary Th2 rest	0.0	0.0	HUVEC IL-11	0.0	0.0
Secondary Tr1 rest	0.0	0.0	Lung Microvascular EC none	0.0	0.0
Primary Th1 act	0.0	0.0	Lung Microvascular EC TNFalpha + IL- 1beta	0.0	0.0
Primary Th2 act	0.0	0.0	Microvascular Dermal EC none	0.0	0.0
Primary Tr1 act	0.0	0.0	Microvascular Dermal EC TNFalpha + IL- 1beta	0.0	0.0
Primary Th1 rest	0.0	0.0	Bronchial epithelium TNFalpha + IL1beta	0.0	0.0
Primary Th2 rest	0.0	0.0	Small airway epithelium none	0.0	0.0
Primary Tr1 rest	0.0	0.0	Small airway epithelium TNFalpha + IL- 1beta	0.0	0.0
CD45RA CD4 lymphocyte act	3.3	5.0	Coronary artery SMC rest	1.0	2.3
CD45RO CD4 lymphocyte act	0.0	0.0	Coronary artery SMC TNFalpha + IL-1beta	3.7	1.2
CD8 lymphocyte act	0.0	0.0	Astrocytes rest	3.2	0.5
Secondary CD8 lymphocyte rest	0.0	0.0	Astrocytes TNFalpha + IL- 1beta	1.0	1.5
Secondary CD8 lymphocyte act	0.0	0.0	KU-812 (Basophil) rest	0.0	0.0
CD4 lymphocyte none	0.0	0.0	KU-812 (Basophil) PMA/ionomycin	0.0	0.0
2ry Th1/Th2/Tr1_anti- CD95 CH11	0.0	0.0	CCD1106 (Keratinocytes) none	0.0	0.0
LAK cells rest	0.0	0.0	CCD1106 (Keratinocytes) TNFalpha + IL- 1beta	0.0	0.0

LAK cells IL-2	0.0	0.0	Liver cirrhosis	1.4	3.8
LAK cells IL-2+IL-12	0.0	0.0	Lupus kidney	0.0	0.8
LAK cells IL-2+IFN gamma	0.0	0.0	NCI-H292 none	0.0	0.0
LAK cells IL-2+ IL-18	0.0	0.0	NCI-H292 IL-4	0.0	2.3
LAK cells PMA/ionomycin	0.0	0.0	NCI-H292 IL-9	0.0	0.5
NK Cells IL-2 rest	0.0	0.0	NCI-H292 IL-13	0.0	1.3
Two Way MLR 3 day	0.0	0.0	NCI-H292 IFN gamma	0.0	0.0
Two Way MLR 5 day	0.0	0.0	HPAEC none	0.0	0.0
Two Way MLR 7 day	0.0	0.0	HPAEC TNF alpha + IL-1 beta	0.0	0.0
PBMC rest	0.0	0.0	Lung fibroblast none	0.0	0.9
PBMC PWM	0.0	0.0	Lung fibroblast TNF alpha + IL-1 beta	0.0	0.0
PBMC PHA-L	0.0	0.0	Lung fibroblast IL-4	0.0	0.0
Ramos (B cell) none	0.0	0.0	Lung fibroblast IL-9	5.7	1.3
Ramos (B cell) ionomycin	0.0	0.0	Lung fibroblast IL-13	1.5	1.5
B lymphocytes PWM	0.0	0.0	Lung fibroblast IFN gamma	0.0	1.7
B lymphocytes CD40L and IL-4	0.0	0.0	Dermal fibroblast CCD1070 rest	12.9	17.2
EOL-1 dbcAMP	0.0	0.0	Dermal fibroblast CCD1070 TNF alpha	18.6	12.0
EOL-1 dbcAMP PMA/ionomycin	0.0	0.0	Dermal fibroblast CCD1070 IL-1 beta	6.1	2.9
Dendritic cells none	0.0	0.0	Dermal fibroblast IFN gamma	0.0	0.0
Dendritic cells LPS	0.0	0.0	Dermal fibroblast IL-4	1.4	0.6
Dendritic cells anti-CD40	0.0	0.0	IBD Colitis 2	0.0	1.4
Monocytes rest	0.0	0.0	IBD Crohn's	0.0	0.0
Monocytes LPS	0.0	0.0	Colon	0.6	0.0
Macrophages rest	0.0	0.0	Lung	4.0	11.7
Macrophages LPS	0.0	0.0	Thymus	100.0	100.0
HUVEC none	0.0	0.0	Kidney	4.2	5.3
HUVEC starved	0.0	0.0			

Table 30. Panel 5D

Tissue Name	Rel. Exp.(%)	Tissue Name	Rel. Exp.(%)
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	Ag2315, Run 169275446		Ag2315, Run 169275446
97457_Patient-02go_adipose	84.1	94709_Donor 2 AM - A_adipose	13.6
97476_Patient-07sk_skeletal muscle	0.6	94710_Donor 2 AM - B_adipose	9.3
97477_Patient-07ut_uterus	0.0	94711_Donor 2 AM - C_adipose	3.6
97478_Patient-07pl_placenta	7.2	94712_Donor 2 AD - A_adipose	8.7
97481_Patient-08sk_skeletal muscle	4.4	94713_Donor 2 AD - B_adipose	17.1
97482_Patient-08ut_uterus	0.5	94714_Donor 2 AD - C_adipose	21.6
97483_Patient-08pl_placenta	6.5	94742_Donor 3 U - A_Mesenchymal Stem Cells	9.0
97486_Patient-09sk_skeletal muscle	0.0	94743_Donor 3 U - B_Mesenchymal Stem Cells	7.3
97487_Patient-09ut_uterus	0.5	94730_Donor 3 AM - A_adipose	14.8
97488_Patient-09pl_placenta	6.1	94731_Donor 3 AM - B_adipose	13.9
97492_Patient-10ut_uterus	0.0	94732_Donor 3 AM - C_adipose	5.9
97493_Patient-10pl_placenta	7.8	94733_Donor 3 AD - A_adipose	5.4
97495_Patient-11go_adipose	100.0	94734_Donor 3 AD - B_adipose	4.7
97496_Patient-11sk_skeletal muscle	0.6	94735_Donor 3 AD - C_adipose	9.3
97497_Patient-11ut_uterus	1.0	77138_Liver_HepG2untreated	6.9
97498_Patient-11pl_placenta	7.3	73556_Heart_Cardiac stromal cells (primary)	0.0
97500_Patient-12go_adipose	61.6	81735_Small Intestine	1.5
97501_Patient-12sk_skeletal muscle	3.2	72409_Kidney_Proximal Convoluted Tubule	0.0
97502_Patient-12ut_uterus	1.4	82685_Small intestine_Duodenum	0.0
97503_Patient-12pl_placenta	1.5	90650_Adrenal_Adrenocortical adenoma	0.0
94721_Donor 2 U - A_Mesenchymal Stem Cells	14.4	72410_Kidney_HRCE	0.0
94722_Donor 2 U - B_Mesenchymal Stem Cells	6.7	72411_Kidney_HRE	0.0
94723_Donor 2 U - C_Mesenchymal Stem	6.0	73139_Uterus_Uterine smooth muscle cells	0.0

Cells			
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Panel 1.3D Summary: Ag1555/2315 Highest expression of the CG50718-01 gene is seen in adipose and the fetal lung (CTs=31.8-34.4). Results from three experiments with two different probe and primer sets produce similar expression profiles. Low but significant expression is also seen in the thyroid. Biologic cross-talk between the thyroid and adipose tissue is believed to be a component of some forms of obesity. Thus, the CG50718-01 gene product may be an important small molecule target for the treatment of obesity or other metabolic disorders.

In addition, the CG50718-01 gene appears to be expressed at significant levels in lung and kidney tissues from both fetal and adult sources, but not in any samples derived from lung or kidney cancer cell lines. Thus, expression of this gene could potentially be used to differentiate between normal lung and kidney tissue and lung and kidney cancer. Furthermore, therapeutic modulation of the CG50718-01 gene product may be beneficial in the treatment of lung and kidney cancers.

Please note that two other experiments with the probe and primer set Ag2315 had low/undetectable levels of expression in all the samples on this panel. (Data not shown.)

Panel 2D Summary: Ag1555/2315 Three experiments with two different probe and primer sets produce results that are in excellent agreement with highest expression of the CG50718-01 gene in normal kidney tissue (CTs=30.7-32.4). There are also significant levels of expression in samples derived from normal lung tissue, a result that is in concordance with the expression seen in Panel 1.3D. This gene appears to be preferentially expressed in healthy tissue, when compared to adjacent cancerous tissue. Thus, expression of the CG50718-01 gene could be used to distinguish normal kidney and lung tissue from malignant kidney and lung tissue. Moreover, therapeutic modulation of this gene, through small molecule drugs, antibodies or protein therapeutics might be of benefit in the treatment of kidney cancer and lung cancer.

Panel 3D Summary: Ag2315 Expression is low/undetectable in all the samples in this panel (CT>35). (Data not shown.)

Panel 4D Summary: Ag1555/Ag2315 The CG50718-01 transcript is detected at significant levels in the thymus (CT 31.48) and at lower levels in dermal fibroblasts (CT 33.91). This transcript encodes a protein that could potentially serve as a marker for thymus tissue and may also be involved in skin homeostasis. Therapeutics designed with the protein encoded by the CG50718-01 transcript could be important for maintaining or restoring normal function to these organs during inflammation.

Panel 5D Summary: Ag2315 is modestly expressed (CT values 31-34) in human adipose tissue and in cultured human adipocytes. This expression is in agreement with the significant levels of expression in adipose detected in Panel 1.3D. Thus, this gene product may be a small molecule target for the treatment of obesity.

5 NOV3

Expression of NOV3 was assessed using the primer-probe set Ag2304, described in Table 31. Results of the RTQ-PCR runs are shown in Tables 32, 33, 34 and 35.

Table 31. Probe Name Ag2304

Primers	Sequences	Length	Start Position	SEQ ID NO:
Forward	5'-accttaagtcctgccaacaatt-3'	22	4100	151
Probe	TET-5'- ttacagagtccaaattgtggatccca-3'- TAMRA	26	4147	152
Reverse	5'-tgatcccttcagaatttgac-3'	21	4173	153

Table 32. CNS neurodegeneration v1.0

Tissue Name	Rel. Exp.(%) Ag2304, Run 206262286	Tissue Name	Rel. Exp.(%) Ag2304, Run 206262286
AD 1 Hippo	0.0	Control (Path) 3 Temporal Ctx	7.3
AD 2 Hippo	38.4	Control (Path) 4 Temporal Ctx	29.5
AD 3 Hippo	8.5	AD 1 Occipital Ctx	16.5
AD 4 Hippo	9.5	AD 2 Occipital Ctx (Missing)	0.0
AD 5 Hippo	100.0	AD 3 Occipital Ctx	8.7
AD 6 Hippo	70.7	AD 4 Occipital Ctx	22.2
Control 2 Hippo	44.8	AD 5 Occipital Ctx	45.1
Control 4 Hippo	13.3	AD 5 Occipital Ctx	0.0
Control (Path) 3 Hippo	0.0	Control 1 Occipital Ctx	4.5
AD 1 Temporal Ctx	25.0	Control 2 Occipital Ctx	58.2
AD 2 Temporal Ctx	39.2	Control 3 Occipital Ctx	18.2
AD 3 Temporal Ctx	7.7	Control 4 Occipital Ctx	7.3
AD 4 Temporal Ctx	0.2	Control (Path) 1 Occipital Ctx	92.7
AD 5 Inf Temporal Ctx	76.8	Control (Path) 2 Occipital Ctx	0.0
AD 5 Sup Temporal Ctx	40.6	Control (Path) 3 Occipital Ctx	3.4

AD 6 Inf Temporal Ctx	49.7	Control (Path) 4 Occipital Ctx	16.7
AD 6 Sup Temporal Ctx	57.4	Control 1 Parietal Ctx	7.1
Control 1 Temporal Ctx	9.2	Control 2 Parietal Ctx	41.8
Control 2 Temporal Ctx	40.9	Control 3 Parietal Ctx	0.0
Control 3 Temporal Ctx	20.6	Control (Path) 1 Parietal Ctx	97.9
Control 3 Temporal Ctx	10.7	Control (Path) 2 Parietal Ctx	29.5
Control (Path) 1 Temporal Ctx	97.3	Control (Path) 3 Parietal Ctx	4.4
Control (Path) 2 Temporal Ctx	52.9	Control (Path) 4 Parietal Ctx	68.3

Table 33. Panel 1.3D

Tissue Name	Rel. Exp.(%) Ag2304, Run 159131830	Tissue Name	Rel. Exp.(%) Ag2304, Run 159131830
Liver adenocarcinoma	6.0	Kidney (fetal)	8.5
Pancreas	1.7	Renal ca. 786-0	7.6
Pancreatic ca. CAPAN 2	2.4	Renal ca. A498	13.2
Adrenal gland	14.9	Renal ca. RXF 393	3.2
Thyroid	6.5	Renal ca. ACHN	3.1
Salivary gland	2.3	Renal ca. UO-31	8.3
Pituitary gland	13.4	Renal ca. TK-10	3.5
Brain (fetal)	7.7	Liver	2.8
Brain (whole)	13.5	Liver (fetal)	5.8
Brain (amygdala)	15.5	Liver ca. (hepatoblast) HepG2	7.3
Brain (cerebellum)	4.6	Lung	19.9
Brain (hippocampus)	100.0	Lung (fetal)	9.9
Brain (substantia nigra)	2.8	Lung ca. (small cell) LX-1	5.4
Brain (thalamus)	10.0	Lung ca. (small cell) NCI-H69	12.3
Cerebral Cortex	25.0	Lung ca. (s.cell var.) SHP-77	12.1
Spinal cord	4.0	Lung ca. (large cell)NCI-H460	3.8
glio/astro U87-MG	21.9	Lung ca. (non-sm. cell) A549	5.9
glio/astro U-118-MG	40.9	Lung ca. (non-s.cell) NCI-H23	13.6
astrocytoma SW1783	9.2	Lung ca. (non-s.cell) HOP-62	7.0
neuro*; met SK-N-AS	65.5	Lung ca. (non-s.cl) NCI-H522	3.4

astrocytoma SF-539	9.8	Lung ca. (squam.) SW 900	6.6
astrocytoma SNB-75	11.9	Lung ca. (squam.) NCI-H596	1.7
glioma SNB-19	9.6	Mammary gland	18.4
glioma U251	6.0	Breast ca.* (pl.ef) MCF-7	6.3
glioma SF-295	6.5	Breast ca.* (pl.ef) MDA-MB-231	34.6
Heart (Fetal)	0.6	Breast ca.* (pl. ef) T47D	5.1
Heart	2.3	Breast ca. BT-549	20.2
Skeletal muscle (Fetal)	11.4	Breast ca. MDA-N	5.7
Skeletal muscle	8.5	Ovary	5.6
Bone marrow	8.5	Ovarian ca. OVCAR-3	7.7
Thymus	7.4	Ovarian ca. OVCAR-4	0.7
Spleen	12.0	Ovarian ca. OVCAR-5	16.7
Lymph node	6.3	Ovarian ca. OVCAR-8	8.6
Colorectal	4.6	Ovarian ca. IGROV-1	2.4
Stomach	8.5	Ovarian ca. (ascites) SK-OV-3	15.5
Small intestine	9.2	Uterus	6.4
Colon ca. SW480	8.0	Placenta	8.1
Colon ca.* SW620 (SW480 met)	5.3	Prostate	3.4
Colon ca. HT29	2.6	Prostate ca.* (bone met) PC-3	5.9
Colon ca. HCT-116	7.4	Testis	18.6
Colon ca. CaCo-2	7.4	Melanoma Hs688(A).T	4.5
CC Well to Mod Diff (ODO3866)	9.2	Melanoma* (met) Hs688(B).T	2.5
Colon ca. HCC-2998	8.6	Melanoma UACC-62	1.6
Gastric ca. (liver met) NCI-N87	30.8	Melanoma M14	0.6
Bladder	2.7	Melanoma LOX IMVI	4.0
Trachea	12.0	Melanoma* (met) SK-MEL-5	2.3
Kidney	3.5	Adipose	7.5

Table 34. Panel 2D

Tissue Name	Rel. Exp.(%) Ag2304, Run 159134494	Tissue Name	Rel. Exp.(%) Ag2304, Run 159134494
Normal Colon	82.9	Kidney Margin 8120608	5.5
CC Well to Mod Diff (ODO3866)	21.3	Kidney Cancer 8120613	17.9
CC Margin (ODO3866)	14.6	Kidney Margin 8120614	13.1

CC Gr.2 rectosigmoid (ODO3868)	10.9	Kidney Cancer 9010320	24.7
CC Margin (ODO3868)	9.9	Kidney Margin 9010321	19.3
CC Mod Diff (ODO3920)	21.5	Normal Uterus	17.6
CC Margin (ODO3920)	27.4	Uterine Cancer 064011	52.5
CC Gr.2 ascend colon (ODO3921)	45.1	Normal Thyroid	22.7
CC Margin (ODO3921)	15.8	Thyroid Cancer	36.1
CC from Partial Hepatectomy (ODO4309) Mets	37.9	Thyroid Cancer A302152	18.2
Liver Margin (ODO4309)	28.9	Thyroid Margin A302153	30.1
Colon mets to lung (OD04451-01)	23.2	Normal Breast	49.7
Lung Margin (OD04451-02)	24.1	Breast Cancer	28.5
Normal Prostate 6546-1	18.4	Breast Cancer (OD04590-01)	51.8
Prostate Cancer (OD04410)	59.9	Breast Cancer Mets (OD04590-03)	64.6
Prostate Margin (OD04410)	67.4	Breast Cancer Metastasis	47.6
Prostate Cancer (OD04720-01)	46.7	Breast Cancer	26.2
Prostate Margin (OD04720-02)	93.3	Breast Cancer	28.9
Normal Lung	100.0	Breast Cancer 9100266	20.2
Lung Met to Muscle (ODO4286)	41.2	Breast Margin 9100265	16.7
Muscle Margin (ODO4286)	47.6	Breast Cancer A209073	38.2
Lung Malignant Cancer (OD03126)	31.9	Breast Margin A2090734	44.8
Lung Margin (OD03126)	64.2	Normal Liver	23.2
Lung Cancer (OD04404)	58.6	Liver Cancer	23.3
Lung Margin (OD04404)	38.2	Liver Cancer 1025	10.5
Lung Cancer (OD04565)	15.8	Liver Cancer 1026	6.7
Lung Margin (OD04565)	26.4	Liver Cancer 6004-T	14.1
Lung Cancer (OD04237-01)	37.6	Liver Tissue 6004-N	9.5
Lung Margin (OD04237-02)	48.0	Liver Cancer 6005-T	6.7
Ocular Mel Met to Liver (ODO4310)	14.9	Liver Tissue 6005-N	6.7
Liver Margin (ODO4310)	13.5	Normal Bladder	49.0
Melanoma Metastasis	36.6	Bladder Cancer	5.7
Lung Margin (OD04321)	50.3	Bladder Cancer	32.5
Normal Kidney	84.7	Bladder Cancer (OD04718-01)	52.1
Kidney Ca, Nuclear grade 2	65.1	Bladder Normal	63.7

(OD04338)		Adjacent (OD04718-03)	
Kidney Margin (OD04338)	46.3	Normal Ovary	6.0
Kidney Ca Nuclear grade 1/2 (OD04339)	33.4	Ovarian Cancer	63.3
Kidney Margin (OD04339)	77.9	Ovarian Cancer (OD04768-07)	43.8
Kidney Ca, Clear cell type (OD04340)	71.7	Ovary Margin (OD04768-08)	14.6
Kidney Margin (OD04340)	57.0	Normal Stomach	30.4
Kidney Ca, Nuclear grade 3 (OD04348)	17.2	Gastric Cancer 9060358	10.4
Kidney Margin (OD04348)	28.9	Stomach Margin 9060359	12.9
Kidney Cancer (OD04622-01)	21.9	Gastric Cancer 9060395	56.3
Kidney Margin (OD04622-03)	4.3	Stomach Margin 9060394	30.4
Kidney Cancer (OD04450-01)	29.5	Gastric Cancer 9060397	33.2
Kidney Margin (OD04450-03)	36.9	Stomach Margin 9060396	8.9
Kidney Cancer 8120607	3.4	Gastric Cancer 064005	53.6

Table 35. Panel 4D

Tissue Name	Rel. Exp.(%) Ag2304, Run 159131012	Tissue Name	Rel. Exp.(%) Ag2304, Run 159131012
Secondary Th1 act	32.5	HUVEC IL-1beta	5.8
Secondary Th2 act	46.7	HUVEC IFN gamma	19.6
Secondary Tr1 act	47.0	HUVEC TNF alpha + IFN gamma	12.2
Secondary Th1 rest	14.5	HUVEC TNF alpha + IL4	9.8
Secondary Th2 rest	27.0	HUVEC IL-11	8.8
Secondary Tr1 rest	23.5	Lung Microvascular EC none	5.8
Primary Th1 act	44.1	Lung Microvascular EC TNFalpha + IL-1beta	12.8
Primary Th2 act	39.2	Microvascular Dermal EC none	20.6
Primary Tr1 act	49.3	Microvascular Dermal EC TNFalpha + IL-1beta	16.0
Primary Th1 rest	95.3	Bronchial epithelium TNFalpha + IL1beta	14.2
Primary Th2 rest	54.7	Small airway epithelium none	7.9
Primary Tr1 rest	29.5	Small airway epithelium TNFalpha + IL-1beta	38.4
CD45RA CD4 lymphocyte act	21.5	Coronary artery SMC rest	25.3
CD45RO CD4	37.1	Coronary artery SMC	12.7

lymphocyte act		TNFalpha + IL-1beta	
CD8 lymphocyte act	20.9	Astrocytes rest	23.0
Secondary CD8 lymphocyte rest	29.1	Astrocytes TNFalpha + IL-1beta	23.7
Secondary CD8 lymphocyte act	22.7	KU-812 (Basophil) rest	4.6
CD4 lymphocyte none	26.6	KU-812 (Basophil) PMA/ionomycin	11.0
2ry Th1/Th2/Tr1_anti-CD95 CH11	34.2	CCD1106 (Keratinocytes) none	15.8
LAK cells rest	41.5	CCD1106 (Keratinocytes) TNFalpha + IL-1beta	5.1
LAK cells IL-2	33.2	Liver cirrhosis	2.8
LAK cells IL-2+IL-12	22.8	Lupus kidney	4.3
LAK cells IL-2+IFN gamma	36.9	NCI-H292 none	34.9
LAK cells IL-2+ IL-18	38.4	NCI-H292 IL-4	38.4
LAK cells PMA/ionomycin	34.2	NCI-H292 IL-9	39.2
NK Cells IL-2 rest	26.6	NCI-H292 IL-13	21.2
Two Way MLR 3 day	53.2	NCI-H292 IFN gamma	20.9
Two Way MLR 5 day	26.2	HPAEC none	11.3
Two Way MLR 7 day	13.3	HPAEC TNF alpha + IL-1 beta	11.7
PBMC rest	14.5	Lung fibroblast none	18.9
PBMC PWM	83.5	Lung fibroblast TNF alpha + IL-1 beta	22.8
PBMC PHA-L	31.9	Lung fibroblast IL-4	25.9
Ramos (B cell) none	11.4	Lung fibroblast IL-9	13.4
Ramos (B cell) ionomycin	34.4	Lung fibroblast IL-13	18.9
B lymphocytes PWM	60.3	Lung fibroblast IFN gamma	46.0
B lymphocytes CD40L and IL-4	16.6	Dermal fibroblast CCD1070 rest	47.0
EOL-1 dbcAMP	34.2	Dermal fibroblast CCD1070 TNF alpha	83.5
EOL-1 dbcAMP PMA/ionomycin	100.0	Dermal fibroblast CCD1070 IL-1 beta	23.7
Dendritic cells none	13.7	Dermal fibroblast IFN gamma	18.3
Dendritic cells LPS	16.5	Dermal fibroblast IL-4	25.2
Dendritic cells anti-CD40	6.3	IBD Colitis 2	2.3
Monocytes rest	23.5	IBD Crohn's	4.3
Monocytes LPS	84.1	Colon	24.5
Macrophages rest	23.3	Lung	23.7
Macrophages LPS	31.4	Thymus	39.0
HUVEC none	15.0	Kidney	44.4

HUVEC starved	30.6		
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CNS_neurodegeneration_v1.0 Summary: Ag2304 Expression of the NOV3 gene in this panel is ubiquitous. While this gene does not show differential expression between Alzheimer's diseased brains and control brains, this panel confirms the expression of this gene in the brains of an independent group of patients. See Panel 1.3d for utility of this gene in the central nervous system.

Panel 1.3D Summary: Ag2304 The NOV3 gene, a homolog of the *Drosophila* pecanex gene, is widely expressed across the samples in this panel, with highest expression in the hippocampus (CT=28.6). In addition, this gene is expressed at moderate to high levels in all CNS regions examined. Expression of this gene in both the mother and developing embryo is critical for normal CNS development. Furthermore, expression of this protein appears to be involved in stem cell fate determination, where removal of this protein increases neural precursor cells. Therefore, downregulation of this gene could be used in neural stem cell research and therapy to control the fate of stem cells and increasing the resulting numbers of post-mitotic neurons.

The NOV3 gene is modestly expressed in a wide variety of metabolic tissues including adipose, adrenal, pancreas, thyroid, pituitary, heart, adult and fetal skeletal muscle, and adult and fetal liver. This widespread expression in tissues with metabolic function suggests that the NOV3 gene product may be important for the pathogenesis, diagnosis, and/or treatment of metabolic disease in any or all of these tissues, including obesity and diabetes.

References:

1. LaBonne SG, Furst A. Differentiation in vitro of neural precursor cells from normal and Pecanex mutant *Drosophila* embryos. *J Neurogenet* 1989 May;5(2):99-104

Early gastrula embryos, lacking both maternally and zygotically expressed activity of the neurogenic pecanex locus, are shown to contain a greater than wild-type number of stably determined neural precursor cells which can differentiate into neurons in culture.

2. LaBonne SG, Sunitha I, Mahowald AP. Molecular genetics of pecanex, a maternal-effect neurogenic locus of *Drosophila melanogaster* that potentially encodes a large transmembrane protein. *Dev Biol* 1989 Nov;136(1):1-16

In the absence of maternal expression of the pecanex gene, the embryo develops severe hyperneuralization similar to that characteristic of Notch mutant embryos. We have extended a previous molecular analysis of the chromosomal interval that encompasses pecanex by using additional deficiencies to localize the locus on the molecular map. RNA blot analysis shows that the locus encodes a rare 9-kb transcript as well as minor transcripts of 3.7 and 2.3 kb. The

Panel 2D Summary: Ag2304 The expression of this gene appears to be highest in a sample derived from normal lung tissue. Thus, the expression of this gene could be used to distinguish normal lung tissue from other tissues in the panel. Of note is the difference in expression between samples derived from ovarian cancer and normal adjacent tissue. This difference in levels of expression is also notable in samples derived from gastric cancer when compared to their normal counterparts. Thus, the expression of this gene could be used to distinguish ovarian or gastric cancer from their normal adjacent tissues. Moreover, therapeutic modulation of this gene, through the use of small molecule drugs, antibodies or protein therapeutics might be of use in the treatment of ovarian or gastric cancer.

Panel 4D Summary: Ag 2304 This NOV3 transcript is detected ubiquitously throughout this panel, with highest expression of this transcript in activated eosinophils (CT=28.1). This indicates an up-regulation of this transcript in these cells upon activation. Eosinophils contribute to the pathology of several atopic diseases such as asthma, atopic dermatitis, and rhinitis. Therefore, modulation of the activity or activation of the protein encoded by the NOV3 gene may be beneficial for the treatment of those diseases. The NOV3 gene is also highly expressed in effector T cells, activated monocytes and dermal fibroblasts upon treatment with TNF- α and IL-1 β . Modulation of the expression of this transcript, which encodes for a Pecanex like molecule, could be beneficial in the treatment of inflammatory diseases associated with T cell activation as well as eosinophil activation including atopic diseases and autoimmune diseases such as rheumatoid arthritis, inflammatory bowel disease and skin inflammation.

NOV4

Expression of gene NOV4 was assessed using the primer-probe set Ag2428, described in Table 36. Results of the RTQ-PCR runs are shown in Tables 37, 38, 39 and 40.

Table 36. Probe Name Ag2428

Primers	Sequences	Length	Start Position	SEQ ID NO:
Forward	5'-gagccagggtgctgtata-3'	19	1419	154
Probe	TET-5'-	26	1439	155

	cctctcaggaacatgctacaaaaatt-3'- TAMRA			
Reverse	5'-tagattgagggcagcagtca-3'	20	1476	156

Table 37. CNS_neurodegeneration_v1.0

Tissue Name	Rel. Exp.(%) Ag2428, Run 206271177	Tissue Name	Rel. Exp.(%) Ag2428, Run 206271177
AD 1 Hippo	7.9	Control (Path) 3 Temporal Ctx	3.5
AD 2 Hippo	22.2	Control (Path) 4 Temporal Ctx	40.3
AD 3 Hippo	12.8	AD 1 Occipital Ctx	18.3
AD 4 Hippo	5.1	AD 2 Occipital Ctx (Missing)	0.0
AD 5 Hippo	100.0	AD 3 Occipital Ctx	7.0
AD 6 Hippo	32.5	AD 4 Occipital Ctx	20.3
Control 2 Hippo	10.9	AD 5 Occipital Ctx	25.0
Control 4 Hippo	17.0	AD 5 Occipital Ctx	16.5
Control (Path) 3 Hippo	6.7	Control 1 Occipital Ctx	6.0
AD 1 Temporal Ctx	16.6	Control 2 Occipital Ctx	21.0
AD 2 Temporal Ctx	23.2	Control 3 Occipital Ctx	23.2
AD 3 Temporal Ctx	9.4	Control 4 Occipital Ctx	6.0
AD 4 Temporal Ctx	25.9	Control (Path) 1 Occipital Ctx	50.3
AD 5 Inf Temporal Ctx	40.1	Control (Path) 2 Occipital Ctx	13.2
AD 5 Sup Temporal Ctx	33.7	Control (Path) 3 Occipital Ctx	1.1
AD 6 Inf Temporal Ctx	35.6	Control (Path) 4 Occipital Ctx	30.4
AD 6 Sup Temporal Ctx	48.3	Control 1 Parietal Ctx	12.4
Control 1 Temporal Ctx	8.0	Control 2 Parietal Ctx	46.0
Control 2 Temporal Ctx	8.5	Control 3 Parietal Ctx	23.7
Control 3 Temporal Ctx	14.7	Control (Path) 1 Parietal Ctx	38.7
Control 3 Temporal Ctx	11.3	Control (Path) 2 Parietal Ctx	20.4
Control (Path) 1 Temporal Ctx	37.6	Control (Path) 3 Parietal Ctx	5.4
Control (Path) 2 Temporal Ctx	34.9	Control (Path) 4 Parietal Ctx	43.2

Table 38. Panel 1.3D

Tissue Name	Rel. Exp.(%) Ag2428, Run 159361380	Tissue Name	Rel. Exp.(%) Ag2428, Run 159361380
Liver adenocarcinoma	10.7	Kidney (fetal)	7.1
Pancreas	2.4	Renal ca. 786-0	6.6
Pancreatic ca. CAPAN 2	6.0	Renal ca. A498	18.8
Adrenal gland	5.3	Renal ca. RXF 393	3.8
Thyroid	2.5	Renal ca. ACHN	1.1
Salivary gland	3.7	Renal ca. UO-31	4.5
Pituitary gland	7.2	Renal ca. TK-10	5.1
Brain (fetal)	5.2	Liver	1.9
Brain (whole)	5.1	Liver (fetal)	11.4
Brain (amygdala)	5.1	Liver ca. (hepatoblast) HepG2	8.0
Brain (cerebellum)	2.7	Lung	8.5
Brain (hippocampus)	17.6	Lung (fetal)	4.7
Brain (substantia nigra)	1.8	Lung ca. (small cell) LX-1	7.5
Brain (thalamus)	4.9	Lung ca. (small cell) NCI-H69	11.9
Cerebral Cortex	2.8	Lung ca. (s.cell var.) SHP-77	25.2
Spinal cord	3.8	Lung ca. (large cell)NCI-H460	8.8
glio/astro U87-MG	12.9	Lung ca. (non-sm. cell) A549	8.3
glio/astro U-118-MG	39.5	Lung ca. (non-s.cell) NCI-H23	18.3
astrocytoma SW1783	5.4	Lung ca. (non-s.cell) HOP-62	6.6
neuro*; met SK-N-AS	100.0	Lung ca. (non-s.cl) NCI-H522	8.4
astrocytoma SF-539	7.6	Lung ca. (squam.) SW 900	9.7
astrocytoma SNB-75	19.8	Lung ca. (squam.) NCI-H596	5.4
glioma SNB-19	12.0	Mammary gland	5.9
glioma U251	11.3	Breast ca.* (pl.ef) MCF-7	10.9
glioma SF-295	7.4	Breast ca.* (pl.ef) MDA-MB-231	66.0
Heart (Fetal)	2.0	Breast ca.* (pl. ef) T47D	9.6
Heart	5.1	Breast ca. BT-549	34.4
Skeletal muscle (Fetal)	8.5	Breast ca. MDA-N	17.7
Skeletal muscle	1.2	Ovary	2.1
Bone marrow	17.8	Ovarian ca. OVCAR-3	10.8
Thymus	5.6	Ovarian ca. OVCAR-4	0.6

Spleen	10.1	Ovarian ca. OVCAR-5	5.6
Lymph node	9.2	Ovarian ca. OVCAR-8	10.0
Colorectal	6.9	Ovarian ca. IGROV-1	2.1
Stomach	7.3	Ovarian ca. (ascites) SK-OV-3	15.1
Small intestine	8.1	Uterus	3.7
Colon ca. SW480	8.5	Placenta	3.8
Colon ca.* SW620 (SW480 met)	13.6	Prostate	6.0
Colon ca. HT29	11.0	Prostate ca.* (bone met) PC-3	5.8
Colon ca. HCT-116	12.9	Testis	9.3
Colon ca. CaCo-2	12.3	Melanoma Hs688(A).T	2.6
CC Well to Mod Diff (ODO3866)	7.6	Melanoma* (met) Hs688(B).T	1.9
Colon ca. HCC-2998	33.0	Melanoma UACC-62	3.8
Gastric ca. (liver met) NCI-N87	25.9	Melanoma M14	5.8
Bladder	10.2	Melanoma LOX IMVI	5.2
Trachea	9.0	Melanoma* (met) SK- MEL-5	10.3
Kidney	2.5	Adipose	6.3

Table 39. Panel 2D

Tissue Name	Rel. Exp.(%) Ag2428, Run 159361727	Tissue Name	Rel. Exp.(%) Ag2428, Run 159361727
Normal Colon	80.1	Kidney Margin 8120608	2.1
CC Well to Mod Diff (ODO3866)	13.7	Kidney Cancer 8120613	15.3
CC Margin (ODO3866)	7.7	Kidney Margin 8120614	6.8
CC Gr.2 rectosigmoid (ODO3868)	25.5	Kidney Cancer 9010320	21.3
CC Margin (ODO3868)	6.6	Kidney Margin 9010321	17.4
CC Mod Diff (ODO3920)	70.2	Normal Uterus	3.2
CC Margin (ODO3920)	30.4	Uterine Cancer 064011	21.3
CC Gr.2 ascend colon (ODO3921)	52.1	Normal Thyroid	9.9
CC Margin (ODO3921)	11.1	Thyroid Cancer	5.8
CC from Partial Hepatectomy (ODO4309) Mets	50.7	Thyroid Cancer A302152	27.7
Liver Margin (ODO4309)	22.7	Thyroid Margin A302153	37.6
Colon mets to lung (OD04451-01)	29.1	Normal Breast	18.7

Lung Margin (OD04451-02)	7.0	Breast Cancer	26.4
Normal Prostate 6546-1	8.8	Breast Cancer (OD04590-01)	75.3
Prostate Cancer (OD04410)	49.3	Breast Cancer Mets (OD04590-03)	87.1
Prostate Margin (OD04410)	41.2	Breast Cancer Metastasis	48.0
Prostate Cancer (OD04720-01)	52.9	Breast Cancer	49.7
Prostate Margin (OD04720-02)	59.5	Breast Cancer	36.3
Normal Lung	81.8	Breast Cancer 9100266	18.4
Lung Met to Muscle (ODO4286)	30.1	Breast Margin 9100265	14.9
Muscle Margin (ODO4286)	13.9	Breast Cancer A209073	55.5
Lung Malignant Cancer (OD03126)	47.3	Breast Margin A2090734	45.1
Lung Margin (OD03126)	41.8	Normal Liver	15.8
Lung Cancer (OD04404)	28.5	Liver Cancer	14.4
Lung Margin (OD04404)	16.7	Liver Cancer 1025	5.7
Lung Cancer (OD04565)	28.3	Liver Cancer 1026	5.7
Lung Margin (OD04565)	14.0	Liver Cancer 6004-T	7.9
Lung Cancer (OD04237-01)	62.4	Liver Tissue 6004-N	8.1
Lung Margin (OD04237-02)	28.3	Liver Cancer 6005-T	5.2
Ocular Mel Met to Liver (ODO4310)	23.5	Liver Tissue 6005-N	0.8
Liver Margin (ODO4310)	11.3	Normal Bladder	81.8
Melanoma Metastasis	40.9	Bladder Cancer	9.2
Lung Margin (OD04321)	26.2	Bladder Cancer	62.0
Normal Kidney	54.3	Bladder Cancer (OD04718-01)	32.8
Kidney Ca, Nuclear grade 2 (OD04338)	40.1	Bladder Normal Adjacent (OD04718-03)	24.8
Kidney Margin (OD04338)	45.7	Normal Ovary	0.8
Kidney Ca Nuclear grade 1/2 (OD04339)	82.9	Ovarian Cancer	51.8
Kidney Margin (OD04339)	45.4	Ovarian Cancer (OD04768-07)	86.5
Kidney Ca, Clear cell type (OD04340)	49.3	Ovary Margin (OD04768-08)	8.5
Kidney Margin (OD04340)	48.0	Normal Stomach	20.7
Kidney Ca, Nuclear grade 3 (OD04348)	24.3	Gastric Cancer 9060358	6.9
Kidney Margin (OD04348)	40.3	Stomach Margin 9060359	13.1
Kidney Cancer (OD04622-01)	10.7	Gastric Cancer 9060395	23.5
Kidney Margin (OD04622-02)	3.1	Stomach Margin	18.9

03)		9060394	
Kidney Cancer (OD04450-01)	24.8	Gastric Cancer 9060397	39.8
Kidney Margin (OD04450-03)	25.5	Stomach Margin 9060396	7.1
Kidney Cancer 8120607	2.7	Gastric Cancer 064005	100.0

Table 40. Panel 4D

Tissue Name	Rel. Exp.(%) Ag2428, Run 159362614	Tissue Name	Rel. Exp.(%) Ag2428, Run 159362614
Secondary Th1 act	26.8	HUVEC IL-1beta	9.2
Secondary Th2 act	34.6	HUVEC IFN gamma	14.1
Secondary Tr1 act	37.6	HUVEC TNF alpha + IFN gamma	8.4
Secondary Th1 rest	10.7	HUVEC TNF alpha + IL4	12.0
Secondary Th2 rest	13.6	HUVEC IL-11	7.9
Secondary Tr1 rest	16.7	Lung Microvascular EC none	10.9
Primary Th1 act	36.9	Lung Microvascular EC TNFalpha + IL-1beta	9.9
Primary Th2 act	48.3	Microvascular Dermal EC none	17.0
Primary Tr1 act	50.7	Microsvascular Dermal EC TNFalpha + IL-1beta	10.6
Primary Th1 rest	74.2	Bronchial epithelium TNFalpha + IL1beta	9.8
Primary Th2 rest	41.5	Small airway epithelium none	3.6
Primary Tr1 rest	28.9	Small airway epithelium TNFalpha + IL-1beta	38.7
CD45RA CD4 lymphocyte act	22.7	Coronery artery SMC rest	9.9
CD45RO CD4 lymphocyte act	31.0	Coronery artery SMC TNFalpha + IL-1beta	4.2
CD8 lymphocyte act	15.9	Astrocytes rest	5.9
Secondary CD8 lymphocyte rest	19.6	Astrocytes TNFalpha + IL-1beta	5.8
Secondary CD8 lymphocyte act	17.9	KU-812 (Basophil) rest	8.7
CD4 lymphocyte none	11.6	KU-812 (Basophil) PMA/ionomycin	31.6
2ry Th1/Th2/Tr1_anti-CD95 CH11	18.8	CCD1106 (Keratinocytes) none	12.3
LAK cells rest	20.4	CCD1106 (Keratinocytes) TNFalpha + IL-1beta	8.4
LAK cells IL-2	27.7	Liver cirrhosis	4.7
LAK cells IL-2+IL-12	20.0	Lupus kidney	2.1
LAK cells IL-2+IFN gamma	38.4	NCI-H292 none	25.5

LAK cells IL-2+ IL-18	43.5	NCI-H292 IL-4	37.1
LAK cells PMA/ionomycin	13.6	NCI-H292 IL-9	36.9
NK Cells IL-2 rest	21.2	NCI-H292 IL-13	15.6
Two Way MLR 3 day	23.8	NCI-H292 IFN gamma	14.1
Two Way MLR 5 day	11.3	HPAEC none	11.1
Two Way MLR 7 day	11.3	HPAEC TNF alpha + IL-1 beta	13.5
PBMC rest	7.9	Lung fibroblast none	10.7
PBMC PWM	60.3	Lung fibroblast TNF alpha + IL-1 beta	5.0
PBMC PHA-L	23.5	Lung fibroblast IL-4	18.6
Ramos (B cell) none	23.5	Lung fibroblast IL-9	13.0
Ramos (B cell) ionomycin	80.7	Lung fibroblast IL-13	11.0
B lymphocytes PWM	100.0	Lung fibroblast IFN gamma	13.6
B lymphocytes CD40L and IL-4	44.8	Dermal fibroblast CCD1070 rest	27.9
EOL-1 dbcAMP	11.0	Dermal fibroblast CCD1070 TNF alpha	82.9
EOL-1 dbcAMP PMA/ionomycin	19.6	Dermal fibroblast CCD1070 IL-1 beta	15.0
Dendritic cells none	9.5	Dermal fibroblast IFN gamma	10.1
Dendritic cells LPS	7.6	Dermal fibroblast IL-4	11.9
Dendritic cells anti-CD40	5.5	IBD Colitis 2	2.8
Monocytes rest	15.8	IBD Crohn's	2.2
Monocytes LPS	11.0	Colon	11.0
Macrophages rest	9.3	Lung	5.3
Macrophages LPS	5.2	Thymus	18.6
HUVEC none	12.2	Kidney	41.8
HUVEC starved	33.0		

CNS_neurodegeneration_v1.0 Summary: Ag2428 While results from this experiment show that this gene is not differentially expressed in the Alzheimer's diseased brain, this panel confirms the expression of this gene at moderate levels in the CNS in an independent group of patients. Please see Panel 1.3D for a discussion of utility of this gene in the central nervous system.

Panel 1.3D Summary: Ag2428 The NOV4 gene is expressed widely across many samples in this panel, with highest expression in a sample derived from a neuroblastoma cell line(CT=29.8). Moreover, there appears to be a cluster of expression associated with breast cancer cell lines. Thus, the expression of this gene could be used to distinguish these samples from others in the panel.

In addition, the NOV4 gene is moderately expressed in a number of metabolic tissues including adipose, adrenal, pituitary, heart, fetal skeletal muscle and fetal liver. Thus, this gene product may be an important small molecule target for the treatment of metabolic disease, including obesity and Type 2 diabetes.

5 This gene is expressed at low levels in the CNS, and is an an aurora-related kinase. The aurora-related kinases are involed in the control of the cell-cycle, and may be useful in the control of cell fate in neural stem cells. This protein may therefore be of usc in stem cell research or therapy.

References:

10 Severson AF, Hamill DR, Carter JC, Schumacher J, Bowerman B. The aurora-related kinase AIR-2 recruits ZEN-4/CeMKLP1 to the mitotic spindle at metaphase and is required for cytokinesis. *Curr Biol* 2000 Oct 5;10(19):1162-71

BACKGROUND: The Aurora/Ipl1p-related kinase AIR-2 is required for mitotic chromosome segregation and cytokinesis in early *Caenorhabditis elegans* embryos. Previous studies have relied on non-conditional mutations or RNA-mediated interference (RNAi) to inactivate AIR-2. It has therefore not been possible to determine whether AIR-2 functions directly in cytokinesis or if the cleavage defect results indirectly from the failure to segregate DNA. One intriguing hypothesis is that AIR-2 acts to localize the mitotic kinesin-like protein ZEN-4 (also known as CeMKLP1), which later functions in cytokinesis. RESULTS: Using conditional alleles, we established that AIR-2 is required at metaphase or early anaphase for normal segregation of chromosomes, localization of ZEN-4, and cytokinesis. ZEN-4 is first required late in cytokinesis, and also functions to maintain cell separation through much of the subsequent interphase. DNA segregation defects alone were not sufficient to disrupt cytokinesis in other mutants, suggesting that AIR-2 acts specifically during cytokinesis through ZEN-4. AIR-2 and ZEN-4 shared similar genetic interactions with the formin homology (FH) protein CYK-1, suggesting that AIR-2 and ZEN-4 function in a single pathway, in parallel to a contractile ring pathway that includes CYK-1. Using in vitro co-immunoprecipitation experiments, we found that AIR-2 and ZEN-4 interact directly. CONCLUSIONS: AIR-2 has two functions during mitosis: one in chromosome segregation, and a second, independent function in cytokinesis through ZEN-4. AIR-2 and ZEN-4 may act in parallel to a second pathway that includes CYK-1.

Panel 2D Summary: Ag2428 The expression of this gene is found widely across a number of samples in this panel. It is found to be highest in a sample derived from a gastric cancer. Of note is the association observed between gastric cancer samples, when compared to

their normal adjacent samples. This association is also notable in ovarian cancer and breast cancer. Thus, the expression of this gene could be used to distinguish gastric cancer, breast cancer and ovarian cancer from their normal adjacent tissues. Moreover, therapeutic modulation of this gene, through the use of small molecule drugs, antibodies or protein therapeutics might
 5 be of benefit in the treatment of gastric, breast or ovarian cancer.

Panel 4D Summary: Ag 2428 This transcript is ubiquitously expressed in all cells throughout the panel. However, the highest expression of this transcript is found in B cells upon activation with the B cell mitogen, PWM. Significant expression of this transcript in the activated Ramos B cell line is consistent with this finding. This transcript encodes an aurora-
 10 related kinase 1 which belongs to a family of oncogenic mitogenic serine threonine kinases (see reference below). Therefore, modulation of the expression of this transcript by small molecules, may be beneficial for the treatment of diseases associated with hyperproliferation of B cells including B cell lymphomas, hyperglobulinemia and autoimmune disease such as lupus and rheumatoid arthritis. This transcript is also expressed in dermal fibroblasts upon
 15 treatment with TNF- α and IL-1 and in primary Th1 cells suggesting that modulation of this transcript may be important in the treatment of T cell mediated diseases and inflammatory skin diseases.

Reference:

1. J Cell Sci 1999 Nov;112 (Pt 21):3591-601. Aurora/Ipl1p-related kinases, a new
 20 oncogenic family of mitotic serine-threonine kinases. Giet R, Prigent C.

CNRS UPR41| Universite de Rennes I, Groupe Cycle Cellulaire, Faculte de Medecine, CS 34317, France.

During the past five years, a growing number of serine-threonine kinases highly homologous to the *Saccharomyces cerevisiae* Ipl1p kinase have been isolated in various
 25 organisms. A *Drosophila melanogaster* homologue, aurora, was the first to be isolated from a multicellular organism. Since then, several related kinases have been found in mammalian cells. They localise to the mitotic apparatus: in the centrosome, at the poles of the bipolar spindle or in the midbody. The kinases are necessary for completion of mitotic events such as centrosome separation, bipolar spindle assembly and chromosome segregation. Extensive
 30 research is now focusing on these proteins because the three human homologues are overexpressed in various primary cancers. Furthermore, overexpression of one of these kinases transforms cells. Because of the myriad of kinases identified, we suggest a generic name: Aurora/Ipl1p-related kinase (AIRK). We denote AIRKs with a species prefix and a number, e.g. HsAIRK1.

NOV5

Expression of gene NOV5 was assessed using the primer-probe set Ag2423, described in Table 41. Results of the RTQ-PCR runs are shown in Tables 42, 43 and 44.

5

Table 41. Probe Name Ag2423

Primers	Sequences	Length	Start Position	SEQ ID NO:
Forward	5'-aactgccactggtgacactt-3'	20	243	157
Probe	TET-5'- cacactcagtggtcggttaaaattactga-3'- TAMRA	28	263	158
Reverse	5'-tgaattcttccaccatgagaa-3'	21	315	159

Table 42. Panel 1.3D

Tissue Name	Rel. Exp.(%) Ag2423, Run 159337657	Tissue Name	Rel. Exp.(%) Ag2423, Run 159337657
Liver adenocarcinoma	25.9	Kidney (fetal)	0.0
Pancreas	8.4	Renal ca. 786-0	11.7
Pancreatic ca. CAPAN 2	7.1	Renal ca. A498	7.2
Adrenal gland	65.1	Renal ca. RXF 393	9.6
Thyroid	4.0	Renal ca. ACHN	8.5
Salivary gland	41.8	Renal ca. UO-31	8.4
Pituitary gland	9.9	Renal ca. TK-10	4.5
Brain (fetal)	75.8	Liver	13.6
Brain (whole)	5.1	Liver (fetal)	28.1
Brain (amygdala)	5.8	Liver ca. (hepatoblast) HepG2	12.9
Brain (cerebellum)	3.8	Lung	21.0
Brain (hippocampus)	66.4	Lung (fetal)	15.4
Brain (substantia nigra)	20.4	Lung ca. (small cell) LX-1	4.9
Brain (thalamus)	7.4	Lung ca. (small cell) NCI-H69	4.6
Cerebral Cortex	52.9	Lung ca. (s.cell var.) SHP-77	14.7
Spinal cord	22.5	Lung ca. (large cell)NCI-H460	15.7
glio/astro U87-MG	11.5	Lung ca. (non-sm. cell) A549	9.8
glio/astro U-118-MG	11.1	Lung ca. (non-s.cell) NCI-H23	12.2
astrocytoma SW1783	15.8	Lung ca. (non-s.cell) HOP-62	18.2
neuro*; met SK-N-AS	10.2	Lung ca. (non-s.cl) NCI-H522	10.7

astrocytoma SF-539	9.5	Lung ca. (squam.) SW 900	8.0
astrocytoma SNB-75	0.0	Lung ca. (squam.) NCI-H596	9.3
glioma SNB-19	16.6	Mammary gland	13.0
glioma U251	5.2	Breast ca.* (pl.ef) MCF-7	3.1
glioma SF-295	0.0	Breast ca.* (pl.ef) MDA-MB-231	8.3
Heart (Fetal)	24.1	Breast ca.* (pl. ef) T47D	4.0
Heart	33.0	Breast ca. BT-549	6.1
Skeletal muscle (Fetal)	6.5	Breast ca. MDA-N	0.0
Skeletal muscle	10.8	Ovary	7.2
Bone marrow	5.7	Ovarian ca. OVCAR-3	16.7
Thymus	0.0	Ovarian ca. OVCAR-4	13.2
Spleen	33.0	Ovarian ca. OVCAR-5	10.6
Lymph node	13.7	Ovarian ca. OVCAR-8	0.0
Colorectal	28.5	Ovarian ca. IGROV-1	9.3
Stomach	4.8	Ovarian ca. (ascites) SK-OV-3	0.0
Small intestine	8.6	Uterus	0.0
Colon ca. SW480	0.0	Placenta	8.0
Colon ca.* SW620 (SW480 met)	4.4	Prostate	0.0
Colon ca. HT29	5.3	Prostate ca.* (bone met) PC-3	0.0
Colon ca. HCT-116	19.9	Testis	0.0
Colon ca. CaCo-2	9.7	Melanoma Hs688(A).T	0.0
CC Well to Mod Diff (ODO3866)	0.0	Melanoma* (met) Hs688(B).T	0.0
Colon ca. HCC-2998	0.0	Melanoma UACC-62	6.6
Gastric ca. (liver met) NCI-N87	0.0	Melanoma M14	5.1
Bladder	100.0	Melanoma LOX IMVI	8.2
Trachea	4.4	Melanoma* (met) SK-MEL-5	8.7
Kidney	25.7	Adipose	79.6

Table 43. Panel 2D

Tissue Name	Rel. Exp.(%) Ag2423, Run 159338041	Tissue Name	Rel. Exp.(%) Ag2423, Run 159338041
Normal Colon	34.6	Kidney Margin 8120608	0.0
CC Well to Mod Diff (ODO3866)	34.2	Kidney Cancer 8120613	0.0
CC Margin (ODO3866)	38.7	Kidney Margin 8120614	0.0

CC Gr.2 rectosigmoid (ODO3868)	9.1	Kidney Cancer 9010320	0.0
CC Margin (ODO3868)	11.0	Kidney Margin 9010321	0.0
CC Mod Diff (ODO3920)	12.9	Normal Uterus	8.9
CC Margin (ODO3920)	17.7	Uterine Cancer 064011	12.2
CC Gr.2 ascend colon (ODO3921)	79.0	Normal Thyroid	2.6
CC Margin (ODO3921)	17.1	Thyroid Cancer	5.6
CC from Partial Hepatectomy (ODO4309) Mets	24.1	Thyroid Cancer A302152	7.7
Liver Margin (ODO4309)	17.8	Thyroid Margin A302153	10.9
Colon mets to lung (OD04451-01)	2.0	Normal Breast	7.2
Lung Margin (OD04451-02)	8.0	Breast Cancer	2.4
Normal Prostate 6546-1	2.8	Breast Cancer (OD04590-01)	16.0
Prostate Cancer (OD04410)	45.4	Breast Cancer Mets (OD04590-03)	19.5
Prostate Margin (OD04410)	27.4	Breast Cancer Metastasis	11.2
Prostate Cancer (OD04720-01)	9.8	Breast Cancer	10.9
Prostate Margin (OD04720-02)	29.3	Breast Cancer	3.6
Normal Lung	38.2	Breast Cancer 9100266	12.9
Lung Met to Muscle (ODO4286)	36.3	Breast Margin 9100265	4.6
Muscle Margin (ODO4286)	9.9	Breast Cancer A209073	15.4
Lung Malignant Cancer (OD03126)	15.7	Breast Margin A2090734	6.1
Lung Margin (OD03126)	12.0	Normal Liver	3.8
Lung Cancer (OD04404)	14.4	Liver Cancer	9.1
Lung Margin (OD04404)	10.1	Liver Cancer 1025	3.8
Lung Cancer (OD04565)	7.4	Liver Cancer 1026	2.7
Lung Margin (OD04565)	0.0	Liver Cancer 6004-T	3.2
Lung Cancer (OD04237-01)	43.8	Liver Tissue 6004-N	3.4
Lung Margin (OD04237-02)	12.9	Liver Cancer 6005-T	3.4
Ocular Mel Met to Liver (ODO4310)	3.0	Liver Tissue 6005-N	1.6
Liver Margin (ODO4310)	4.1	Normal Bladder	36.9
Melanoma Metastasis	33.2	Bladder Cancer	10.0
Lung Margin (OD04321)	23.7	Bladder Cancer	22.4
Normal Kidney	12.4	Bladder Cancer (OD04718-01)	100.0
Kidney Ca, Nuclear grade 2	6.8	Bladder Normal	13.1

(OD04338)		Adjacent (OD04718-03)	
Kidney Margin (OD04338)	6.2	Normal Ovary	3.0
Kidney Ca Nuclear grade 1/2 (OD04339)	20.7	Ovarian Cancer	18.2
Kidney Margin (OD04339)	11.8	Ovarian Cancer (OD04768-07)	47.6
Kidney Ca, Clear cell type (OD04340)	29.9	Ovary Margin (OD04768-08)	6.1
Kidney Margin (OD04340)	11.0	Normal Stomach	6.2
Kidney Ca, Nuclear grade 3 (OD04348)	5.8	Gastric Cancer 9060358	0.0
Kidney Margin (OD04348)	9.8	Stomach Margin 9060359	42.3
Kidney Cancer (OD04622-01)	0.0	Gastric Cancer 9060395	37.4
Kidney Margin (OD04622-03)	0.0	Stomach Margin 9060394	47.0
Kidney Cancer (OD04450-01)	7.5	Gastric Cancer 9060397	76.3
Kidney Margin (OD04450-03)	5.4	Stomach Margin 9060396	3.1
Kidney Cancer 8120607	0.0	Gastric Cancer 064005	35.6

Table 44. Panel 4D

Tissue Name	Rel. Exp.(%) Ag2423, Run 159338325	Tissue Name	Rel. Exp.(%) Ag2423, Run 159338325
Secondary Th1 act	2.1	HUVEC IL-1beta	1.9
Secondary Th2 act	4.8	HUVEC IFN gamma	0.0
Secondary Tr1 act	1.4	HUVEC TNF alpha + IFN gamma	0.0
Secondary Th1 rest	7.5	HUVEC TNF alpha + IL4	0.0
Secondary Th2 rest	10.2	HUVEC IL-11	0.0
Secondary Tr1 rest	2.0	Lung Microvascular EC none	4.7
Primary Th1 act	2.3	Lung Microvascular EC TNFalpha + IL-1beta	3.5
Primary Th2 act	100.0	Microvascular Dermal EC none	8.0
Primary Tr1 act	3.4	Microvascular Dermal EC TNFalpha + IL-1beta	15.3
Primary Th1 rest	0.9	Bronchial epithelium TNFalpha + IL1beta	1.3
Primary Th2 rest	3.8	Small airway epithelium none	3.6
Primary Tr1 rest	1.4	Small airway epithelium TNFalpha + IL-1beta	0.0
CD45RA CD4 lymphocyte act	1.6	Coronary artery SMC rest	0.0
CD45RO CD4	0.0	Coronary artery SMC	0.0

lymphocyte act		TNFalpha + IL-1beta	
CD8 lymphocyte act	5.2	Astrocytes rest	5.1
Secondary CD8 lymphocyte rest	0.0	Astrocytes TNFalpha + IL-1beta	0.0
Secondary CD8 lymphocyte act	1.1	KU-812 (Basophil) rest	0.0
CD4 lymphocyte none	2.2	KU-812 (Basophil) PMA/ionomycin	2.1
2ry Th1/Th2/Tr1_anti-CD95 CH11	1.5	CCD1106 (Keratinocytes) none	1.5
LAK cells rest	7.6	CCD1106 (Keratinocytes) TNFalpha + IL-1beta	2.0
LAK cells IL-2	5.8	Liver cirrhosis	2.1
LAK cells IL-2+IL-12	1.4	Lupus kidney	4.8
LAK cells IL-2+IFN gamma	0.0	NCI-H292 none	1.6
LAK cells IL-2+ IL-18	1.7	NCI-H292 IL-4	6.6
LAK cells PMA/ionomycin	1.7	NCI-H292 IL-9	0.0
NK Cells IL-2 rest	0.9	NCI-H292 IL-13	0.0
Two Way MLR 3 day	0.0	NCI-H292 IFN gamma	1.3
Two Way MLR 5 day	1.8	HPAEC none	0.0
Two Way MLR 7 day	8.5	HPAEC TNF alpha + IL-1 beta	1.4
PBMC rest	1.8	Lung fibroblast none	0.9
PBMC PWM	1.8	Lung fibroblast TNF alpha + IL-1 beta	6.0
PBMC PHA-L	3.7	Lung fibroblast IL-4	6.3
Ramos (B cell) none	2.0	Lung fibroblast IL-9	1.0
Ramos (B cell) ionomycin	0.0	Lung fibroblast IL-13	0.9
B lymphocytes PWM	0.0	Lung fibroblast IFN gamma	0.8
B lymphocytes CD40L and IL-4	0.0	Dermal fibroblast CCD1070 rest	2.2
EOL-1 dbcAMP	4.2	Dermal fibroblast CCD1070 TNF alpha	2.0
EOL-1 dbcAMP PMA/ionomycin	0.0	Dermal fibroblast CCD1070 IL-1 beta	0.0
Dendritic cells none	2.3	Dermal fibroblast IFN gamma	0.0
Dendritic cells LPS	4.3	Dermal fibroblast IL-4	0.0
Dendritic cells anti-CD40	0.0	IBD Colitis 2	3.1
Monocytes rest	1.7	IBD Crohn's	1.8
Monocytes LPS	28.3	Colon	0.0
Macrophages rest	20.7	Lung	0.0
Macrophages LPS	1.1	Thymus	2.0
HUVEC none	2.0	Kidney	3.7

Panel 1.3D Summary: Ag2423 This gene is expressed exclusively in a sample derived from bladder tissue. Thus, the expression of this gene could be used to distinguish bladder tissue from other tissues in the panel.

Panel 4D Summary: Ag2423 The expression of this gene is highest and almost exclusive to primary activated Th2 cells (CT 32.6). Very low expression of this transcript is found in activated LPS and macrophages (CT 34.9). This transcript encodes for a 26s proteasome like protein which is an essential component of the cellular protein degradation machinery. Some studies (reference 1) indicate a potential role for proteasomes in the regulation of signal transduction in T and B lymphocytes. This novel 26S proteasome may be involved in a more specific Th2 signalling pathway. Therefore, this gene product may be useful as a potential therapeutic target for attenuation of hyperactive Th2 response such as observed in allergic diseases (rhinitis, atopic skin diseases, asthma).

25 Biochim Biophys Acta 1999 Jan 6;1453(1):92-104 Proteasome participates in the alteration of signal transduction in T and B lymphocytes following trauma-hemorrhage. Samy TS, Schwacha MG, Chung CS, Cioffi WG, Bland KI, Chaudry IH.

Proteasomes are essential components of the cellular protein degradation machinery. They are nonlysosomal and their participation is critical for (1) the removal of short lived proteins involved in metabolic regulation and cell proliferation, (2) the control of the activities of regulators involved in gene transcription, such as nuclear factor-kappa B (NF-kappa B) and signal transducer and activator of transcription (STAT1), and (3) processing of antigenic peptides for MHC class I presentation. Trauma-hemorrhage induces profound immunosuppression which is characterized by reduced splenocyte proliferation, interleukin (IL)-2 and interferon (IFN)-gamma productive capacity, increased activation of transcription

factors NF-kappa B and STAT1 in splenic T lymphocytes, reduced macrophage antigen presentation capacity and inordinate release of proinflammatory cytokines, such as IL-6 and tumor necrosis factor-alpha. Furthermore, it appears that the activity of several regulatory proteins involved in immune function is altered by trauma-hemorrhage. Since proteasomes are involved in regulation and removal of regulatory proteins, we hypothesized that trauma-hemorrhage alters proteasomal activity in splenic lymphocytes. The data showed that activities of 26s proteasome from CD3+CD4+ and CD3+CD8+ splenic T lymphocytes were enhanced following trauma-hemorrhage which was associated with increased expression of NF-kappa B and STAT1. On the other hand, trauma-hemorrhage attenuated the activity of 26s proteasome from splenic B lymphocytes which was restored upon IFN-gamma stimulation and correlated with increased expression of NF-kappa B. These studies indicate a potential role for proteasomes in the regulation of signal transduction in splenic T and B lymphocytes following trauma-hemorrhage, and also suggest them as potential therapeutic targets for attenuation of immune suppression associated with this form of injury.

NOV6

Expression of gene NOV6 was assessed using the primer-probe sets Ag1508, Ag1586, Ag2011 and Ag2284, described in Tables 45, 46, 47 and 48. Results of the RTQ-PCR runs are shown in Tables 49, 50, 51, 52, 53 and 54.

Table 45. Probe Name Ag1508

Primers	Sequences	Length	Start Position	SEQ ID NO:
Forward	5'-atttggctatcccttcagggtt-3'	21	238	160
Probe	TET-5'-cggatccaatatgagatgccccctct-3'-TAMRA	25	263	161
Reverse	5'-gtcttggagctggactcttcat-3'	22	291	162

Table 46. Probe Name Ag1586

Primers	Sequences	Length	Start Position	SEQ ID NO:
Forward	5'-accaggatgagtttgtgtcatc-3'	22	1583	163
Probe	TET-5'-ctcaagatcccttcggacacgctgt-3'-TAMRA	25	1609	164
Reverse	5'-tgcggaagctgtacacatagta-3'	22	1657	165

Table 47. Probe Name Ag2011

Primers	Sequences	Length	Start Position	SEQ ID NO:
Forward	5'-accaggatgagtttgtgtcatc-3'	22	1583	166
Probe	TET-5'-ctcaagatcccttcggacacgctgt-3'-TAMRA	25	1609	167

Reverse	5'-tgcggaagctgtacacatagta-3'	22	1657	168
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Table 48. Probe Name Ag2284

Primers	Sequences	Length	Start Position	SEQ ID NO"
Forward	5'-tagttatctacctgcgcttcca-3'	22	399	169
Probe	TET-5'- tctacacagagaacaaacgcttcccg-3'- TAMRA	26	426	170
Reverse	5'-gaagggtgaaggagacagtcaca-3'	22	466	171

Table 49. Panel 1.2

Tissue Name	Rel. Exp.(%) Ag1508, Run 141937122	Tissue Name	Rel. Exp.(%) Ag1508, Run 141937122
Endothelial cells	0.0	Renal ca. 786-0	0.0
Heart (Fetal)	0.9	Renal ca. A498	0.0
Pancreas	0.1	Renal ca. RXF 393	0.0
Pancreatic ca. CAPAN 2	0.0	Renal ca. ACHN	0.0
Adrenal Gland	2.7	Renal ca. UO-31	0.0
Thyroid	0.1	Renal ca. TK-10	0.0
Salivary gland	0.9	Liver	0.3
Pituitary gland	0.0	Liver (fetal)	0.1
Brain (fetal)	0.0	Liver ca. (hepatoblast) HepG2	0.0
Brain (whole)	0.0	Lung	0.0
Brain (amygdala)	0.0	Lung (fetal)	0.0
Brain (cerebellum)	0.1	Lung ca. (small cell) LX-1	0.0
Brain (hippocampus)	0.1	Lung ca. (small cell) NCI-H69	0.0
Brain (thalamus)	0.0	Lung ca. (s.cell var.) SHP-77	0.0
Cerebral Cortex	0.3	Lung ca. (large cell)NCI-H460	0.0
Spinal cord	0.0	Lung ca. (non-sm. cell) A549	0.0
glio/astro U87-MG	0.0	Lung ca. (non-s.cell) NCI-H23	0.0
glio/astro U-118-MG	0.1	Lung ca. (non-s.cell) HOP-62	0.0
astrocytoma SW1783	0.0	Lung ca. (non-s.cl) NCI-H522	9.4
neuro*; met SK-N-AS	0.0	Lung ca. (squam.) SW 900	0.2
astrocytoma SF-539	0.0	Lung ca. (squam.) NCI-H596	0.0
astrocytoma SNB-75	0.0	Mammary gland	0.0
glioma SNB-19	0.0	Breast ca.* (pl.ef) MCF-7	0.0

glioma U251	0.0	Breast ca.* (pl.ef) MDA-MB-231	0.0
glioma SF-295	0.0	Breast ca.* (pl. ef) T47D	0.0
Heart	10.7	Breast ca. BT-549	0.0
Skeletal Muscle	100.0	Breast ca. MDA-N	0.0
Bone marrow	0.1	Ovary	0.5
Thymus	0.0	Ovarian ca. OVCAR-3	0.0
Spleen	0.0	Ovarian ca. OVCAR-4	0.0
Lymph node	0.0	Ovarian ca. OVCAR-5	0.0
Colorectal	0.0	Ovarian ca. OVCAR-8	0.0
Stomach	0.1	Ovarian ca. IGROV-1	0.0
Small intestine	0.2	Ovarian ca. (ascites) SK-OV-3	0.0
Colon ca. SW480	0.0	Uterus	0.2
Colon ca.* SW620 (SW480 met)	0.0	Placenta	0.0
Colon ca. HT29	0.0	Prostate	0.4
Colon ca. HCT-116	0.1	Prostate ca.* (bone met) PC-3	0.0
Colon ca. CaCo-2	0.0	Testis	0.2
CC Well to Mod Diff (ODO3866)	0.0	Melanoma Hs688(A).T	0.0
Colon ca. HCC-2998	0.0	Melanoma* (met) Hs688(B).T	0.0
Gastric ca. (liver met) NCI-N87	0.0	Melanoma UACC-62	0.1
Bladder	0.2	Melanoma M14	0.0
Trachea	0.0	Melanoma LOX IMVI	0.0
Kidney	8.9	Melanoma* (met) SK- MEL-5	0.0
Kidney (fetal)	0.6		

Table 50. Panel 1.3D

Tissue Name	Rel. Exp.(%) Ag1586, Run 146473155	Rel. Exp.(%) Ag2011, Run 147816085	Rel. Exp.(%) Ag2284, Run 167985231	Tissue Name	Rel. Exp.(%) Ag1586, Run 146473155	Rel. Exp.(%) Ag2011, Run 147816085	Rel. Exp.(%) Ag2284, Run 167985231
Liver adenocarcinoma	29.9	37.6	0.2	Kidney (fetal)	3.8	3.7	1.6
Pancreas	1.7	0.7	0.3	Renal ca. 786-0	6.1	11.7	0.0
Pancreatic ca. CAPAN 2	6.3	9.6	0.0	Renal ca. A498	25.0	25.9	0.0
Adrenal gland	2.6	2.5	0.5	Renal ca. RXF 393	4.5	5.0	0.0
Thyroid	2.5	1.8	1.2	Renal ca. ACHN	8.8	11.3	0.0

Salivary gland	1.9	2.2	0.4	Renal ca. UO-31	15.0	15.0	0.0
Pituitary gland	0.9	1.5	0.1	Renal ca. TK-10	4.4	4.6	0.0
Brain (fetal)	12.2	13.1	0.0	Liver	0.2	0.1	0.4
Brain (whole)	9.7	10.7	0.2	Liver (fetal)	0.7	0.8	0.1
Brain (amygdala)	9.5	9.9	0.2	Liver ca. (hepatoblast) HepG2	16.8	12.8	0.1
Brain (cerebellum)	3.3	2.3	0.1	Lung	5.0	5.1	0.0
Brain (hippocampus)	24.7	21.0	0.1	Lung (fetal)	7.4	8.1	0.1
Brain (substantia nigra)	0.9	1.3	0.1	Lung ca. (small cell) LX-1	16.8	12.1	0.0
Brain (thalamus)	4.7	3.7	0.1	Lung ca. (small cell) NCI-H69	18.4	23.7	0.0
Cerebral Cortex	75.8	71.2	0.2	Lung ca. (s.cell var.) SHP-77	8.5	7.2	0.0
Spinal cord	2.0	2.4	0.1	Lung ca. (large cell)NCI- H460	10.7	10.1	0.0
glio/astro U87- MG	15.3	17.9	0.0	Lung ca. (non-sm. cell) A549	3.2	4.1	0.0
glio/astro U- 118-MG	38.2	41.2	0.2	Lung ca. (non-s.cell) NCI-H23	23.2	24.7	0.5
astrocytoma SW1783	8.3	10.4	0.1	Lung ca. (non-s.cell) HOP-62	18.9	15.7	0.0
neuro*; met SK-N-AS	23.5	24.3	0.0	Lung ca. (non-s.cl) NCI-H522	5.6	7.5	8.1
astrocytoma SF- 539	19.6	38.4	0.0	Lung ca. (squam.) SW 900	13.0	13.1	0.2
astrocytoma SNB-75	44.4	45.1	0.1	Lung ca. (squam.) NCI-H596	6.5	5.7	0.0
glioma SNB-19	26.2	12.2	0.0	Mammary gland	11.5	9.3	0.2
glioma U251	16.4	16.2	0.1	Breast ca.* (pl.ef) MCF- 7	14.1	14.4	0.0
glioma SF-295	26.4	36.9	0.0	Breast ca.* (pl.ef)	82.9	87.1	0.0

				MDA-MB-231			
Heart (Fetal)	80.7	95.3	1.8	Breast ca.* (pl. ef) T47D	6.1	4.6	0.1
Heart	2.8	1.9	2.3	Breast ca. BT-549	13.6	11.2	0.2
Skeletal muscle (Fetal)	85.3	87.7	100.0	Breast ca. MDA-N	28.1	31.6	0.0
Skeletal muscle	2.1	2.4	88.3	Ovary	20.9	19.5	0.8
Bone marrow	0.6	0.3	0.2	Ovarian ca. OVCAR-3	33.0	40.1	0.0
Thymus	2.6	2.3	0.0	Ovarian ca. OVCAR-4	5.5	5.4	0.0
Spleen	2.9	2.6	0.0	Ovarian ca. OVCAR-5	10.9	13.1	0.1
Lymph node	5.1	5.2	0.1	Ovarian ca. OVCAR-8	17.4	18.3	0.1
Colorectal	5.2	3.9	0.0	Ovarian ca. IGROV-1	4.5	5.3	0.0
Stomach	3.7	5.6	0.2	Ovarian ca. (ascites) SK- OV-3	25.7	22.4	0.1
Small intestine	1.6	1.3	0.2	Uterus	2.7	2.4	1.0
Colon ca. SW480	45.4	55.5	0.1	Placenta	6.7	10.2	0.2
Colon ca.* SW620 (SW480 met)	11.3	11.1	0.0	Prostate	0.4	1.4	0.2
Colon ca. HT29	13.3	13.3	0.0	Prostate ca.* (bone met) PC-3	8.4	11.3	0.0
Colon ca. HCT- 116	10.5	10.5	0.2	Testis	8.1	8.5	1.1
Colon ca. CaCo-2	24.0	23.0	0.1	Melanoma Hs688(A).T	59.0	86.5	0.0
CC Well to Mod Diff (ODO3866)	19.1	16.6	0.1	Melanoma* (met) Hs688(B).T	100.0	100.0	0.0
Colon ca. HCC- 2998	25.7	20.3	0.0	Melanoma UACC-62	17.6	19.5	0.1
Gastric ca. (liver met) NCI- N87	59.9	62.9	0.1	Melanoma M14	16.3	21.9	0.0
Bladder	1.8	4.6	0.2	Melanoma LOX IMVI	3.6	5.8	0.0
Trachea	6.9	5.6	0.1	Melanoma* (met) SK- MEL-5	12.9	22.1	0.0
Kidney	0.8	0.7	2.8	Adipose	5.6	4.5	0.7

Table 51. Panel 2.2

Tissue Name	Rel. Exp.(%) Ag2011, Run 174154748	Tissue Name	Rel. Exp.(%) Ag2011, Run 174154748
Normal Colon	24.7	Kidney Margin (OD04348)	68.3
Colon cancer (OD06064)	48.6	Kidney malignant cancer (OD06204B)	25.0
Colon Margin (OD06064)	4.9	Kidney normal adjacent tissue (OD06204E)	7.4
Colon cancer (OD06159)	9.3	Kidney Cancer (OD04450-01)	34.4
Colon Margin (OD06159)	19.5	Kidney Margin (OD04450-03)	18.4
Colon cancer (OD06297-04)	11.7	Kidney Cancer 8120613	9.7
Colon Margin (OD06297-015)	12.5	Kidney Margin 8120614	18.8
CC Gr.2 ascend colon (ODO3921)	17.3	Kidney Cancer 9010320	16.2
CC Margin (ODO3921)	14.2	Kidney Margin 9010321	13.8
Colon cancer metastasis (OD06104)	8.6	Kidney Cancer 8120607	37.1
Lung Margin (OD06104)	8.3	Kidney Margin 8120608	7.0
Colon mets to lung (OD04451-01)	23.0	Normal Uterus	21.9
Lung Margin (OD04451-02)	32.8	Uterine Cancer 064011	13.7
Normal Prostate	4.8	Normal Thyroid	2.4
Prostate Cancer (OD04410)	4.9	Thyroid Cancer	8.1
Prostate Margin (OD04410)	8.8	Thyroid Cancer A302152	35.4
Normal Ovary	32.3	Thyroid Margin A302153	8.7
Ovarian cancer (OD06283-03)	32.1	Normal Breast	29.7
Ovarian Margin (OD06283-07)	13.8	Breast Cancer	11.9
Ovarian Cancer	19.9	Breast Cancer	47.6
Ovarian cancer (OD06145)	9.2	Breast Cancer (OD04590-01)	25.5
Ovarian Margin (OD06145)	8.6	Breast Cancer Mets (OD04590-03)	38.4
Ovarian cancer (OD06455-03)	13.0	Breast Cancer Metastasis	30.1
Ovarian Margin (OD06455-07)	2.1	Breast Cancer	41.5
Normal Lung	27.2	Breast Cancer 9100266	9.2
Invasive poor diff. lung adeno (ODO4945-01)	28.5	Breast Margin 9100265	18.2

Lung Margin (ODO4945-03)	15.0	Breast Cancer A209073	14.9
Lung Malignant Cancer (OD03126)	30.4	Breast Margin A2090734	37.6
Lung Margin (OD03126)	15.9	Breast cancer (OD06083)	55.9
Lung Cancer (OD05014A)	39.5	Breast cancer node metastasis (OD06083)	48.6
Lung Margin (OD05014B)	22.1	Normal Liver	10.4
Lung cancer (OD06081)	23.7	Liver Cancer 1026	9.1
Lung Margin (OD06081)	16.8	Liver Cancer 1025	20.7
Lung Cancer (OD04237-01)	9.0	Liver Cancer 6004-T	12.2
Lung Margin (OD04237-02)	41.5	Liver Tissue 6004-N	8.0
Ocular Mel Met to Liver (ODO4310)	100.0	Liver Cancer 6005-T	36.6
Liver Margin (ODO4310)	4.2	Liver Tissue 6005-N	25.0
Melanoma Metastasis	47.0	Liver Cancer	4.5
Lung Margin (OD04321)	28.1	Normal Bladder	18.7
Normal Kidney	12.3	Bladder Cancer	17.2
Kidney Ca, Nuclear grade 2 (OD04338)	18.3	Bladder Cancer	72.7
Kidney Margin (OD04338)	18.0	Normal Stomach	33.4
Kidney Ca Nuclear grade 1/2 (OD04339)	83.5	Gastric Cancer 9060397	9.6
Kidney Margin (OD04339)	10.4	Stomach Margin 9060396	10.4
Kidney Ca, Clear cell type (OD04340)	22.2	Gastric Cancer 9060395	7.6
Kidney Margin (OD04340)	12.7	Stomach Margin 9060394	19.6
Kidney Ca, Nuclear grade 3 (OD04348)	15.7	Gastric Cancer 064005	17.4

Table 52. Panel 2D

Tissue Name	Rel. Exp.(%) Ag1508, Run 144982575	Rel. Exp.(%) Ag1586, Run 162624476	Tissue Name	Rel. Exp.(%) Ag1508, Run 144982575	Rel. Exp.(%) Ag1586, Run 162624476
Normal Colon	2.2	34.9	Kidney Margin 8120608	11.3	14.2
CC Well to Mod Diff (ODO3866)	0.1	28.3	Kidney Cancer 8120613	3.6	30.4
CC Margin (ODO3866)	1.4	9.2	Kidney Margin 8120614	11.0	17.7
CC Gr.2 rectosigmoid (ODO3868)	0.1	25.9	Kidney Cancer 9010320	0.7	57.0
CC Margin	0.6	4.7	Kidney Margin	12.0	40.9

(ODO3868)			9010321		
CC Mod Diff (ODO3920)	0.1	55.5	Normal Uterus	2.8	10.4
CC Margin (ODO3920)	1.1	14.2	Uterine Cancer 064011	0.6	28.9
CC Gr.2 ascend colon (ODO3921)	0.1	62.9	Normal Thyroid	15.1	8.4
CC Margin (ODO3921)	0.6	12.1	Thyroid Cancer	7.1	16.7
CC from Partial Hepatectomy (ODO4309) Mets	0.3	41.5	Thyroid Cancer A302152	0.9	24.7
Liver Margin (ODO4309)	2.4	13.6	Thyroid Margin A302153	3.1	17.7
Colon mets to lung (OD04451-01)	0.2	18.0	Normal Breast	0.3	60.3
Lung Margin (OD04451-02)	0.4	25.5	Breast Cancer	0.0	24.1
Normal Prostate 6546-1	3.3	17.0	Breast Cancer (OD04590-01)	0.2	47.0
Prostate Cancer (OD04410)	3.4	33.7	Breast Cancer Mets (OD04590-03)	0.7	72.7
Prostate Margin (OD04410)	0.5	28.9	Breast Cancer Metastasis	0.0	37.4
Prostate Cancer (OD04720-01)	0.3	33.7	Breast Cancer	0.2	36.9
Prostate Margin (OD04720-02)	2.6	45.7	Breast Cancer	0.1	65.1
Normal Lung	0.7	80.7	Breast Cancer 9100266	0.4	39.8
Lung Met to Muscle (ODO4286)	0.3	100.0	Breast Margin 9100265	0.3	31.2
Muscle Margin (ODO4286)	100.0	21.5	Breast Cancer A209073	0.2	49.0
Lung Malignant Cancer (OD03126)	0.3	57.8	Breast Margin A2090734	0.0	44.8
Lung Margin (OD03126)	0.4	61.6	Normal Liver	1.6	4.5
Lung Cancer (OD04404)	0.1	70.2	Liver Cancer	0.9	2.6
Lung Margin (OD04404)	0.3	34.2	Liver Cancer 1025	1.1	4.7
Lung Cancer (OD04565)	0.0	87.7	Liver Cancer 1026	1.0	18.3
Lung Margin (OD04565)	0.8	23.8	Liver Cancer 6004-T	2.3	7.6
Lung Cancer	0.2	41.5	Liver Tissue	0.3	12.0

(OD04237-01)			6004-N		
Lung Margin (OD04237-02)	0.5	34.2	Liver Cancer 6005-T	0.7	12.1
Ocular Mel Met to Liver (ODO4310)	1.3	97.3	Liver Tissue 6005-N	1.6	5.7
Liver Margin (ODO4310)	3.2	5.0	Normal Bladder	0.9	38.2
Melanoma Metastasis	0.0	87.7	Bladder Cancer	0.0	21.3
Lung Margin (OD04321)	0.6	56.3	Bladder Cancer	0.1	46.0
Normal Kidney	18.8	30.1	Bladder Cancer (OD04718-01)	0.2	96.6
Kidney Ca, Nuclear grade 2 (OD04338)	7.5	46.7	Bladder Normal Adjacent (OD04718-03)	2.9	29.5
Kidney Margin (OD04338)	6.0	14.8	Normal Ovary	1.1	21.5
Kidney Ca Nuclear grade 1/2 (OD04339)	11.3	52.1	Ovarian Cancer	0.3	73.7
Kidney Margin (OD04339)	14.2	20.3	Ovarian Cancer (OD04768-07)	0.0	48.3
Kidney Ca, Clear cell type (OD04340)	2.5	49.0	Ovary Margin (OD04768-08)	0.2	18.8
Kidney Margin (OD04340)	11.4	23.2	Normal Stomach	0.9	13.9
Kidney Ca, Nuclear grade 3 (OD04348)	0.9	42.6	Gastric Cancer 9060358	0.3	6.7
Kidney Margin (OD04348)	9.3	28.9	Stomach Margin 9060359	0.3	13.2
Kidney Cancer (OD04622-01)	0.4	50.7	Gastric Cancer 9060395	1.3	28.3
Kidney Margin (OD04622-03)	1.7	8.6	Stomach Margin 9060394	0.4	18.0
Kidney Cancer (OD04450-01)	6.2	21.8	Gastric Cancer 9060397	0.4	45.4
Kidney Margin (OD04450-03)	6.1	18.2	Stomach Margin 9060396	0.0	10.4
Kidney Cancer 8120607	0.9	25.0	Gastric Cancer 064005	0.5	48.3

Table 53. Panel 4.1D

Tissue Name	Rel. Exp.(%) Ag2284, Run 170069125	Tissue Name	Rel. Exp.(%) Ag2284, Run 170069125
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Secondary Th1 act	0.0	HUVEC IL-1beta	0.0
Secondary Th2 act	1.0	HUVEC IFN gamma	0.0
Secondary Tr1 act	0.0	HUVEC TNF alpha + IFN gamma	0.0
Secondary Th1 rest	0.7	HUVEC TNF alpha + IL4	0.0
Secondary Th2 rest	0.5	HUVEC IL-11	0.0
Secondary Tr1 rest	0.0	Lung Microvascular EC none	0.0
Primary Th1 act	0.0	Lung Microvascular EC TNFalpha + IL-1beta	0.0
Primary Th2 act	0.7	Microvascular Dermal EC none	0.0
Primary Tr1 act	0.0	Microsvascular Dermal EC TNFalpha + IL-1beta	0.0
Primary Th1 rest	0.0	Bronchial epithelium TNFalpha + IL1beta	1.0
Primary Th2 rest	0.0	Small airway epithelium none	0.0
Primary Tr1 rest	0.0	Small airway epithelium TNFalpha + IL-1beta	0.0
CD45RA CD4 lymphocyte act	7.5	Coronary artery SMC rest	0.0
CD45RO CD4 lymphocyte act	0.0	Coronary artery SMC TNFalpha + IL-1beta	0.0
CD8 lymphocyte act	0.0	Astrocytes rest	1.9
Secondary CD8 lymphocyte rest	0.0	Astrocytes TNFalpha + IL-1beta	3.2
Secondary CD8 lymphocyte act	0.0	KU-812 (Basophil) rest	0.0
CD4 lymphocyte none	0.0	KU-812 (Basophil) PMA/ionomycin	0.9
2ry Th1/Th2/Tr1_anti-CD95 CH11	1.2	CCD1106 (Keratinocytes) none	0.0
LAK cells rest	0.8	CCD1106 (Keratinocytes) TNFalpha + IL-1beta	0.0
LAK cells IL-2	0.0	Liver cirrhosis	2.2
LAK cells IL-2+IL-12	0.4	NCI-H292 none	0.8
LAK cells IL-2+IFN gamma	0.0	NCI-H292 IL-4	0.0
LAK cells IL-2+ IL-18	0.0	NCI-H292 IL-9	0.0
LAK cells PMA/ionomycin	1.5	NCI-H292 IL-13	0.0
NK Cells IL-2 rest	1.3	NCI-H292 IFN gamma	0.0
Two Way MLR 3 day	1.3	HPAEC none	0.0
Two Way MLR 5 day	1.8	HPAEC TNF alpha + IL-1 beta	0.0
Two Way MLR 7 day	0.0	Lung fibroblast none	27.9
PBMC rest	0.0	Lung fibroblast TNF alpha + IL-1 beta	4.7

PBMC PWM	0.9	Lung fibroblast IL-4	19.3
PBMC PHA-L	0.0	Lung fibroblast IL-9	32.3
Ramos (B cell) none	0.0	Lung fibroblast IL-13	11.4
Ramos (B cell) ionomycin	0.0	Lung fibroblast IFN gamma	9.9
B lymphocytes PWM	0.8	Dermal fibroblast CCD1070 rest	43.2
B lymphocytes CD40L and IL-4	0.0	Dermal fibroblast CCD1070 TNF alpha	31.0
EOL-1 dbcAMP	0.0	Dermal fibroblast CCD1070 IL-1 beta	7.4
EOL-1 dbcAMP PMA/ionomycin	0.0	Dermal fibroblast IFN gamma	5.8
Dendritic cells none	0.0	Dermal fibroblast IL-4	38.4
Dendritic cells LPS	0.5	Dermal Fibroblasts rest	24.7
Dendritic cells anti-CD40	0.9	Neutrophils TNFa+LPS	0.0
Monocytes rest	0.0	Neutrophils rest	0.0
Monocytes LPS	2.4	Colon	1.0
Macrophages rest	8.9	Lung	7.3
Macrophages LPS	0.0	Thymus	3.1
HUVEC none	0.0	Kidney	100.0
HUVEC starved	0.0		

Table 54. Panel 4D

Tissue Name	Rel. Exp.(%) Ag2011, Run 160997385	Tissue Name	Rel. Exp.(%) Ag2011, Run 160997385
Secondary Th1 act	4.7	HUVEC IL-1beta	2.0
Secondary Th2 act	6.4	HUVEC IFN gamma	4.0
Secondary Tr1 act	8.6	HUVEC TNF alpha + IFN gamma	5.0
Secondary Th1 rest	0.6	HUVEC TNF alpha + IL4	8.4
Secondary Th2 rest	1.7	HUVEC IL-11	3.5
Secondary Tr1 rest	1.7	Lung Microvascular EC none	13.0
Primary Th1 act	14.0	Lung Microvascular EC TNFalpha + IL-1beta	15.3
Primary Th2 act	7.7	Microvascular Dermal EC none	23.2
Primary Tr1 act	12.9	Microvascular Dermal EC TNFalpha + IL-1beta	17.3
Primary Th1 rest	3.3	Bronchial epithelium TNFalpha + IL1beta	4.5
Primary Th2 rest	2.3	Small airway epithelium none	16.0
Primary Tr1 rest	2.0	Small airway epithelium TNFalpha + IL-1beta	100.0
CD45RA CD4	6.5	Coronary artery SMC rest	15.7

lymphocyte act			
CD45RO CD4 lymphocyte act	5.3	Coronary artery SMC TNFalpha + IL-1beta	11.1
CD8 lymphocyte act	3.3	Astrocytes rest	25.3
Secondary CD8 lymphocyte rest	7.2	Astrocytes TNFalpha + IL-1beta	21.6
Secondary CD8 lymphocyte act	3.0	KU-812 (Basophil) rest	8.4
CD4 lymphocyte none	1.6	KU-812 (Basophil) PMA/ionomycin	39.5
2ry Th1/Th2/Tr1_anti-CD95 CH11	0.3	CCD1106 (Keratinocytes) none	35.1
LAK cells rest	19.1	CCD1106 (Keratinocytes) TNFalpha + IL-1beta	5.9
LAK cells IL-2	3.1	Liver cirrhosis	0.9
LAK cells IL-2+IL-12	6.5	Lupus kidney	1.3
LAK cells IL-2+IFN gamma	9.8	NCI-H292 none	42.3
LAK cells IL-2+ IL-18	5.9	NCI-H292 IL-4	90.1
LAK cells PMA/ionomycin	8.7	NCI-H292 IL-9	58.2
NK Cells IL-2 rest	1.7	NCI-H292 IL-13	33.9
Two Way MLR 3 day	9.3	NCI-H292 IFN gamma	30.4
Two Way MLR 5 day	7.4	HPAEC none	5.8
Two Way MLR 7 day	2.0	HPAEC TNF alpha + IL-1 beta	12.9
PBMC rest	1.7	Lung fibroblast none	23.8
PBMC PWM	12.5	Lung fibroblast TNF alpha + IL-1 beta	10.7
PBMC PHA-L	5.4	Lung fibroblast IL-4	59.0
Ramos (B cell) none	0.5	Lung fibroblast IL-9	40.6
Ramos (B cell) ionomycin	0.9	Lung fibroblast IL-13	31.0
B lymphocytes PWM	15.6	Lung fibroblast IFN gamma	65.5
B lymphocytes CD40L and IL-4	5.8	Dermal fibroblast CCD1070 rest	37.4
EOL-1 dbcAMP	3.5	Dermal fibroblast CCD1070 TNF alpha	50.0
EOL-1 dbcAMP PMA/ionomycin	60.3	Dermal fibroblast CCD1070 IL-1 beta	19.6
Dendritic cells none	17.6	Dermal fibroblast IFN gamma	15.0
Dendritic cells LPS	32.5	Dermal fibroblast IL-4	43.8
Dendritic cells anti-CD40	21.0	IBD Colitis 2	0.3
Monocytes rest	0.1	IBD Crohn's	0.8
Monocytes LPS	8.4	Colon	5.3
Macrophages rest	34.2	Lung	15.0

Macrophages LPS	11.3	Thymus	5.8
HUVEC none	6.5	Kidney	11.4
HUVEC starved	9.3		

Panel 1.2 Summary: Ag1508 The expression of the NOV6 gene is highest in a sample derived from skeletal muscle (CT = 19.5). Thus, this gene could be used to distinguish skeletal muscle from other tissues. Expression of the NOV6 gene is also high in kidney (CT = 23).

The NOV6 gene is also moderately expressed in other metabolically relevant tissues including heart, adrenal gland, pancreas, thyroid, pituitary gland, and liver (CT values from 29-32). The widespread expression of the NOV6 gene in tissues with metabolic function suggests a role in metabolic disorders such as obesity and diabetes.

The NOV6 gene is moderately expressed in the brain in at least the thalamus, hippocampus, cerebellum, amygdala and is highly expressed in the cerebral cortex, suggesting that this gene product has functional significance in the CNS. Please see Panel 1.3D for potential utility of this gene in the central nervous system.

Panel 1.3D Summary: Ag1586/2011/Ag2284 Two experiments with the same probe and primer set produce results that are in excellent agreement. The NOV6 gene appears to be expressed largely in cancer cell lines, with highest expression in a melanoma cell line (CTs=26-28). Of note is the expression associated with colon cancer cell lines and melanoma cell lines. Thus, the expression of this gene could be used to distinguish these samples from other samples on the panel. Moreover, therapeutic modulation of this gene, through the use of small molecule drugs, antibodies or protein therapeutics might be of use in the treatment of colon cancer or melanoma.

The NOV6 gene is modestly expressed (CT values = 31-34) in a variety of metabolic tissues including pancreas, adrenal, thyroid, pituitary, fetal liver, and adipose. Thus, this gene product may be an antibody target for the treatment of metabolic disease, including obesity and diabetes, in any or all of these tissues. Furthermore, the NOV6 is expressed at higher levels in fetal (CT values = 26-28) versus adult heart (CT values = 31-33), and in fetal (CT values = 26-28) versus adult skeletal muscle (CT values = 32-33), and may be used to differentiate between the adult and fetal sources of these tissues. Furthermore, the higher levels of expression in the fetal tissues suggest that the NOV6 gene product may be involved in the development of heart and skeletal muscle tissue. Thus, therapeutic modulation of the expression or function of the protein encoded by the NOV6 gene may be beneficial in the treatment of diseases that result in weak or dystrophic heart or skeletal muscle tissue, including ardiomyopathy, atherosclerosis, hypertension, congenital heart defects, aortic

stenosis, atrial septal defect (ASD), atrioventricular (A-V) canal defect, ductus arteriosus ,
pulmonary stenosis, subaortic stenosis, ventricular septal defect (VSD), valve diseases,
muscular dystrophy, Lesch-Nyhan syndrome, and myasthenia gravis.

This gene represents a novel protein with homology to a plexin that is expressed at
5 moderate to high levels in all brain regions examined. Plexins act as receptors for semaphorins
in the CNS. The interactions of the semaphorins and their receptors are critical for axon
guidance. Therefore, this gene product may be useful as a drug target in clinical conditions
where axonal growth and/or compensatory synaptogenesis are desirable (spinal cord or head
trauma, stroke, or neurodegenerative diseases such as Alzheimer's, Parkinson's, or
10 Huntington's disease).

References:

1. Pasterkamp RJ, Ruitenberg MJ, Verhaagen J. Semaphorins and their receptors in
olfactory axon guidance. *Cell Mol Biol (Noisy-le-grand)* 1999 Sep;45(6):763-79

The mammalian olfactory system is capable of discriminating among a large variety of
15 odor molecules and is therefore essential for the identification of food, enemies and mating
partners. The assembly and maintenance of olfactory connectivity have been shown to depend
on the combinatorial actions of a variety of molecular signals, including extracellular matrix,
cell adhesion and odorant receptor molecules. Recent studies have identified semaphorins and
their receptors as putative molecular cues involved in olfactory pathfinding, plasticity and
20 regeneration. The semaphorins comprise a large family of secreted and transmembrane axon
guidance proteins, being either repulsive or attractive in nature. Neuropilins were shown to
serve as receptors for secreted class 3 semaphorins, whereas members of the plexin family are
receptors for class 1 and V (viral) semaphorins. The present review will discuss a role for
semaphorins and their receptors in the establishment and maintenance of olfactory
25 connectivity.

2. Murakami Y, Suto F, Shimizu M, Shinoda T, Kameyama T, Fujisawa H.
Differential expression of plexin-A subfamily members in the mouse nervous system. *Dev*
Dyn 2001 Mar;220(3):246-58

Plexins comprise a family of transmembrane proteins (the plexin family) which are
30 expressed in nervous tissues. Some plexins have been shown to interact directly with secreted
or transmembrane semaphorins, while plexins belonging to the A subfamily are suggested to
make complexes with other membrane proteins, neuropilins, and propagate chemorepulsive
signals of secreted semaphorins of class 3 into cells or neurons. Despite that much information
has been gathered on the plexin-semaphorin interaction, the role of plexins in the nervous

system is not well understood. To gain insight into the functions of plexins in the nervous system, we analyzed spatial and temporal expression patterns of three members of the plexin-A subfamily (plexin-A1, -A2, and -A3) in the developing mouse nervous system by in situ hybridization analysis in combination with immunohistochemistry. We show that the three

5 plexins are differentially expressed in sensory receptors or neurons in a developmentally regulated manner, suggesting that a particular plexin or set of plexins is shared by neuronal elements and functions as the receptor for semaphorins to regulate neuronal development.

Panel 2.2 Summary: Ag2011 The expression of this gene appears to be highest in a sample derived from a melanoma metastasis. In addition, there is substantial expression in

10 another melanoma sample. This expression is concordant with the expression detected in Panel 1.3D. Thus, the expression of this gene could be used to distinguish melanoma from other cancer types in this panel. Moreover, therapeutic modulation of this gene, through the use of small molecule drugs, antibodies or protein therapeutics might be of use in the treatment of melanoma.

15 **Panel 2D Summary:** Ag1508/Ag1586 Expression of the SC126413398_A gene in this panel is highest in a sample of muscle tissue adjacent to a metastatic cancer and in a metastasis of lung cancer.

Panel 4.1D Summary: Ag2284 Significant expression in this panel is limited to kidney. This observation is consistent with what was observed in other panels. Therefore,

20 therapeutic drugs designed against the SC126413398_A gene product may be important for regulating the function of the kidney.

Panel 4D Summary: Ag2011 Significant expression of this transcript is found in small airway epithelium upon treatment with the pro-inflammatory cytokines TNF- α and IL-1 β (CT= 26.5), the muco-epidermoid cell line H 292 treated with IL-4 or IL-9, and in lung

25 fibroblasts treated with IFN- γ or IL-4. The constitutive expression of this transcript in these tissues is highly up-regulated by pro-inflammatory cytokines or in conditions reflecting a Th2 mediated mechanism. Therefore, modulation of the expression of the protein encoded by this transcript could be useful for the treatment of lung inflammatory diseases that result from infection of the lung (bronchitis, pneumonia) and for the treatment of Th2-mediated lung

30 disease such as asthma or COPD. Significant expression of this transcript is also found in eosinophils upon PMA and ionomycin treatment, conditions that lead to production of eosinophil specific mediators. This production could contribute to the pathologies associated with asthma, other atopic diseases and inflammatory bowel disease. This gene encodes a novel protein with homology to members of the plexin family, a family of transmembrane proteins

which act as receptors for semaphorins. In neurons, semaphorins provide essential attractive and repulsive cues that are necessary for axon guidance. The description of the interaction of plexin with tyrosine kinase in the fetal lung suggests that this protein may play a role not only in morphogenesis but also in proliferation of activation. (See reference below.) Therefore, modulation of the expression of this protein by either antibody or small molecules could be beneficial for the treatment of inflammatory lung, bowel and skin diseases.

Reference:

1. Cell 1999 Oct 1;99(1):71-80

Plexins are a large family of receptors for transmembrane, secreted, and GPI-anchored semaphorins in vertebrates.

Tamagnone L, Artigiani S, Chen H, He Z, Ming GI, Song H, Chedotal A, Winberg ML, Goodman CS, Poo M, Tessier-Lavigne M, Comoglio PM.

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ltamagnone@ircc.unito.it

In Drosophila, plexin A is a functional receptor for semaphorin-1a. Here we show that the human plexin gene family comprises at least nine members in four subfamilies. Plexin-B1 is a receptor for the transmembrane semaphorin Sema4D (CD100), and plexin-C1 is a receptor for the GPI-anchored semaphorin Sema7A (Sema-K1). Secreted (class 3) semaphorins do not bind directly to plexins, but rather plexins associate with neuropilins, coreceptors for these semaphorins. Plexins are widely expressed: in neurons, the expression of a truncated plexin-A1 protein blocks axon repulsion by Sema3A. The cytoplasmic domain of plexins associates with a tyrosine kinase activity. Plexins may also act as ligands mediating repulsion in epithelial cells in vitro. We conclude that plexins are receptors for multiple (and perhaps all) classes of semaphorins, either alone or in combination with neuropilins, and trigger a novel signal transduction pathway controlling cell repulsion

PMID: 10520995

NOV7

Expression of gene NOV7 was assessed using the primer-probe sets Ag2262 and Ag2316, described in Tables 55 and 56. Results of the RTQ-PCR runs are shown in Tables 57, 58 and 59.

Table 55. Probe Name Ag2262

Primers	Sequences	Length	Start Position	SEQ ID NO:
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Forward	5'-gacctggtgtacatggagga-3'	20	761	172
Probe	TET-5' - cttctgccggcccagcaagtact-3' - TAMRA	23	790	173
Reverse	5'-gagcacaccctacctgctg-3'	19	822	174

Table 56. Probe Name Ag2316

Primers	Sequences	Length	Start Position	SEQ ID NO:
Forward	5'-gtccaagagaggaaacaagga-3'	21	457	175
Probe	TET-5' - cacaatacccacgtgggcatcaag-3' - TAMRA	24	500	176
Reverse	5'-gtcctgaggccactcttcac-3'	20	527	177

Table 57. Panel 1.3D

Tissue Name	Rel. Exp.(%) Ag2262, Run 150719071	Rel. Exp.(%) Ag2262, Run 167966858	Rel. Exp.(%) Ag2316, Run 162185396	Tissue Name	Rel. Exp.(%) Ag2262, Run 150719071	Rel. Exp.(%) Ag2262, Run 167966858	Rel. Exp.(%) Ag2316, Run 162185396
Liver adenocarcinoma	0.0	6.7	0.0	Kidney (fetal)	24.0	100.0	50.0
Pancreas	0.0	0.0	0.0	Renal ca. 786-0	0.0	0.0	0.0
Pancreatic ca. CAPAN 2	0.0	0.0	0.0	Renal ca. A498	0.0	12.6	0.0
Adrenal gland	1.9	0.0	0.0	Renal ca. RXF 393	0.0	0.0	0.0
Thyroid	2.2	0.0	0.0	Renal ca. ACHN	0.0	0.0	0.0
Salivary gland	0.3	0.0	0.0	Renal ca. UO-31	0.2	0.0	0.0
Pituitary gland	0.0	8.0	0.0	Renal ca. TK-10	0.0	0.0	0.0
Brain (fetal)	0.0	1.0	0.0	Liver	0.0	0.0	0.0
Brain (whole)	5.2	0.0	26.2	Liver (fetal)	0.0	0.0	0.0
Brain (amygdala)	6.8	3.8	11.5	Liver ca. (hepatoblast) HepG2	0.0	0.0	0.0
Brain (cerebellum)	1.0	6.4	0.0	Lung	6.8	0.0	19.3
Brain (hippocampus)	16.5	0.0	0.0	Lung (fetal)	8.5	0.0	6.8
Brain (substantia nigra)	2.0	0.0	0.0	Lung ca. (small cell) LX-1	0.0	0.0	0.0
Brain (thalamus)	4.9	11.2	57.0	Lung ca. (small cell) NCI-H69	0.3	0.0	0.0
Cerebral Cortex	2.5	13.3	3.3	Lung ca.	2.5	6.9	0.0

				(s.cell var.) SHP-77			
Spinal cord	3.3	9.2	6.8	Lung ca. (large cell)NCI-H460	0.0	0.0	0.0
glio/astro U87-MG	0.0	0.0	0.0	Lung ca. (non-sm. cell) A549	0.0	6.4	0.0
glio/astro U-118-MG	0.0	0.0	0.0	Lung ca. (non-s.cell) NCI-H23	0.0	0.0	0.0
astrocytoma SW1783	0.0	0.0	0.0	Lung ca. (non-s.cell) HOP-62	0.0	0.0	0.0
neuro*; met SK-N-AS	0.0	0.0	0.0	Lung ca. (non-s.cl) NCI-H522	2.8	0.0	0.0
astrocytoma SF-539	0.0	0.0	0.0	Lung ca. (squam.) SW 900	0.0	0.0	0.0
astrocytoma SNB-75	0.0	0.0	0.0	Lung ca. (squam.) NCI-H596	0.0	0.0	0.0
glioma SNB-19	0.0	0.0	0.0	Mammary gland	0.0	0.0	0.0
glioma U251	0.0	0.0	0.0	Breast ca.* (pl.ef) MCF-7	0.0	0.0	0.0
glioma SF-295	0.0	0.0	0.0	Breast ca.* (pl.ef) MDA-MB-231	0.0	0.0	0.0
Heart (Fetal)	2.0	0.0	33.4	Breast ca.* (pl. ef) T47D	0.0	0.0	0.0
Heart	0.0	6.7	9.6	Breast ca. BT-549	0.0	0.0	0.0
Skeletal muscle (Fetal)	2.5	0.0	8.2	Breast ca. MDA-N	1.0	0.0	0.0
Skeletal muscle	0.0	0.0	0.0	Ovary	0.0	0.0	6.4
Bone marrow	0.9	0.0	0.0	Ovarian ca. OVCAR-3	0.0	0.0	0.0
Thymus	0.0	0.0	0.0	Ovarian ca. OVCAR-4	0.0	0.0	0.0
Spleen	100.0	65.5	100.0	Ovarian ca. OVCAR-5	0.0	0.0	0.0
Lymph node	0.0	0.0	0.0	Ovarian ca. OVCAR-8	0.0	0.0	0.0
Colorectal	10.8	19.8	0.0	Ovarian ca. IGROV-1	0.0	0.0	0.0

Stomach	2.7	0.0	0.0	Ovarian ca. (ascites) SK-OV-3	0.0	0.0	0.0
Small intestine	6.4	0.0	0.0	Uterus	0.0	0.0	0.0
Colon ca. SW480	0.0	0.0	0.0	Placenta	0.6	7.1	0.0
Colon ca.* SW620 (SW480 met)	1.2	0.0	0.0	Prostate	0.0	1.8	4.9
Colon ca. HT29	0.0	0.0	0.0	Prostate ca.* (bone met) PC-3	0.0	0.0	0.0
Colon ca. HCT-116	0.0	0.0	0.0	Testis	1.7	0.0	7.2
Colon ca. CaCo-2	2.5	6.6	0.0	Melanoma Hs688(A).T	0.0	0.0	0.0
CC Well to Mod Diff (ODO3866)	0.0	0.0	0.0	Melanoma* (met) Hs688(B).T	0.0	0.0	0.0
Colon ca. HCC-2998	0.0	0.0	0.0	Melanoma UACC-62	0.0	0.0	0.0
Gastric ca. (liver met) NCI-N87	0.0	14.7	0.0	Melanoma M14	0.0	0.0	0.0
Bladder	0.0	6.5	16.2	Melanoma LOX IMVI	0.0	0.0	0.0
Trachea	5.0	0.0	6.0	Melanoma* (met) SK-MEL-5	0.0	0.0	0.0
Kidney	14.9	7.9	31.0	Adipose	0.0	0.0	7.6

Table 58. Panel 2D

Tissue Name	Rel. Exp.(%) Ag2262, Run 150943107	Tissue Name	Rel. Exp.(%) Ag2262, Run 150943107
Normal Colon	14.2	Kidney Margin 8120608	24.0
CC Well to Mod Diff (ODO3866)	14.2	Kidney Cancer 8120613	0.0
CC Margin (ODO3866)	0.0	Kidney Margin 8120614	46.3
CC Gr.2 rectosigmoid (ODO3868)	0.0	Kidney Cancer 9010320	0.0
CC Margin (ODO3868)	0.0	Kidney Margin 9010321	16.5
CC Mod Diff (ODO3920)	0.0	Normal Uterus	16.4
CC Margin (ODO3920)	0.8	Uterine Cancer 064011	0.0
CC Gr.2 ascend colon (ODO3921)	0.0	Normal Thyroid	15.6
CC Margin (ODO3921)	0.9	Thyroid Cancer	0.0
CC from Partial	0.0	Thyroid Cancer	6.8

Hepatectomy (ODO4309) Mets		A302152	
Liver Margin (ODO4309)	1.1	Thyroid Margin A302153	0.0
Colon mets to lung (OD04451-01)	7.3	Normal Breast	9.3
Lung Margin (OD04451-02)	0.0	Breast Cancer	0.0
Normal Prostate 6546-1	18.6	Breast Cancer (OD04590-01)	4.8
Prostate Cancer (OD04410)	10.2	Breast Cancer Mets (OD04590-03)	8.5
Prostate Margin (OD04410)	0.0	Breast Cancer Metastasis	0.0
Prostate Cancer (OD04720- 01)	0.0	Breast Cancer	7.2
Prostate Margin (OD04720- 02)	9.8	Breast Cancer	0.0
Normal Lung	22.5	Breast Cancer 9100266	0.7
Lung Met to Muscle (ODO4286)	6.1	Breast Margin 9100265	0.0
Muscle Margin (ODO4286)	0.0	Breast Cancer A209073	0.0
Lung Malignant Cancer (OD03126)	5.4	Breast Margin A2090734	0.0
Lung Margin (OD03126)	0.0	Normal Liver	0.0
Lung Cancer (OD04404)	7.6	Liver Cancer	0.0
Lung Margin (OD04404)	3.8	Liver Cancer 1025	5.6
Lung Cancer (OD04565)	0.0	Liver Cancer 1026	2.4
Lung Margin (OD04565)	0.0	Liver Cancer 6004-T	0.0
Lung Cancer (OD04237-01)	0.0	Liver Tissue 6004-N	8.7
Lung Margin (OD04237-02)	6.9	Liver Cancer 6005-T	0.0
Ocular Mel Met to Liver (ODO4310)	1.1	Liver Tissue 6005-N	0.0
Liver Margin (ODO4310)	28.5	Normal Bladder	0.0
Melanoma Metastasis	0.0	Bladder Cancer	0.0
Lung Margin (OD04321)	0.0	Bladder Cancer	18.3
Normal Kidney	100.0	Bladder Cancer (OD04718-01)	0.0
Kidney Ca, Nuclear grade 2 (OD04338)	15.2	Bladder Normal Adjacent (OD04718-03)	0.0
Kidney Margin (OD04338)	40.3	Normal Ovary	0.0
Kidney Ca Nuclear grade 1/2 (OD04339)	0.0	Ovarian Cancer	7.5
Kidney Margin (OD04339)	50.0	Ovarian Cancer (OD04768-07)	0.0
Kidney Ca, Clear cell type (OD04340)	0.0	Ovary Margin (OD04768-08)	0.0
Kidney Margin (OD04340)	31.2	Normal Stomach	13.8
Kidney Ca, Nuclear grade 3	0.0	Gastric Cancer 9060358	0.0

(OD04348)			
Kidney Margin (OD04348)	29.9	Stomach Margin 9060359	0.0
Kidney Cancer (OD04622-01)	0.0	Gastric Cancer 9060395	0.0
Kidney Margin (OD04622-03)	58.6	Stomach Margin 9060394	0.0
Kidney Cancer (OD04450-01)	0.0	Gastric Cancer 9060397	0.0
Kidney Margin (OD04450-03)	95.9	Stomach Margin 9060396	0.0
Kidney Cancer 8120607	0.0	Gastric Cancer 064005	0.0

Table 59. Panel 4D

Tissue Name	Rel. Exp.(%) Ag2262, Run 150981162	Rel. Exp.(%) Ag2316, Run 164037437	Tissue Name	Rel. Exp.(%) Ag2262, Run 150981162	Rel. Exp.(%) Ag2316, Run 164037437
Secondary Th1 act	0.0	0.0	HUVEC IL-1beta	0.0	0.0
Secondary Th2 act	0.0	0.0	HUVEC IFN gamma	0.0	0.0
Secondary Tr1 act	0.0	0.0	HUVEC TNF alpha + IFN gamma	11.6	0.0
Secondary Th1 rest	0.0	0.0	HUVEC TNF alpha + IL4	0.0	0.0
Secondary Th2 rest	0.0	0.0	HUVEC IL-11	8.7	0.0
Secondary Tr1 rest	0.0	0.0	Lung Microvascular EC none	0.0	0.0
Primary Th1 act	0.0	0.0	Lung Microvascular EC TNFalpha + IL-1beta	0.0	0.0
Primary Th2 act	0.0	0.0	Microvascular Dermal EC none	0.0	0.0
Primary Tr1 act	1.8	0.0	Microvascular Dermal EC TNFalpha + IL-1beta	0.0	0.0
Primary Th1 rest	0.0	0.0	Bronchial epithelium TNFalpha + IL1beta	0.0	0.0
Primary Th2 rest	0.0	0.0	Small airway epithelium none	0.0	0.0
Primary Tr1 rest	0.0	0.0	Small airway epithelium TNFalpha + IL-1beta	0.0	0.0
CD45RA CD4 lymphocyte act	0.0	0.0	Coronary artery SMC rest	0.0	0.0
CD45RO CD4 lymphocyte act	0.0	0.0	Coronary artery SMC TNFalpha +	0.0	0.0

			IL-1beta		
CD8 lymphocyte act	0.0	0.0	Astrocytes rest	0.0	0.0
Secondary CD8 lymphocyte rest	0.0	0.0	Astrocytes TNFalpha + IL-1beta	0.0	0.0
Secondary CD8 lymphocyte act	0.0	0.0	KU-812 (Basophil) rest	0.0	25.3
CD4 lymphocyte none	0.0	0.0	KU-812 (Basophil) PMA/ionomycin	0.0	0.0
2ry Th1/Th2/Tr1_anti-CD95 CH11	0.0	0.0	CCD1106 (Keratinocytes) none	0.0	0.0
LAK cells rest	0.0	0.0	CCD1106 (Keratinocytes) TNFalpha + IL-1beta	0.0	0.0
LAK cells IL-2	0.0	0.0	Liver cirrhosis	0.0	0.0
LAK cells IL-2+IL-12	0.0	0.0	Lupus kidney	0.0	21.9
LAK cells IL-2+IFN gamma	17.3	0.0	NCI-H292 none	0.0	0.0
LAK cells IL-2+ IL-18	0.0	0.0	NCI-H292 IL-4	0.0	0.0
LAK cells PMA/ionomycin	0.0	0.0	NCI-H292 IL-9	0.0	0.0
NK Cells IL-2 rest	0.0	0.0	NCI-H292 IL-13	0.0	0.0
Two Way MLR 3 day	0.0	0.0	NCI-H292 IFN gamma	0.0	0.0
Two Way MLR 5 day	17.1	0.0	HPAEC none	0.0	0.0
Two Way MLR 7 day	0.0	0.0	HPAEC TNF alpha + IL-1 beta	1.3	0.0
PBMC rest	0.0	0.0	Lung fibroblast none	0.0	0.0
PBMC PWM	0.0	0.0	Lung fibroblast TNF alpha + IL-1 beta	0.0	0.0
PBMC PHA-L	0.0	0.0	Lung fibroblast IL-4	0.0	0.0
Ramos (B cell) none	0.0	0.0	Lung fibroblast IL-9	0.0	0.0
Ramos (B cell) ionomycin	0.0	0.0	Lung fibroblast IL-13	0.0	0.0
B lymphocytes PWM	0.0	0.0	Lung fibroblast IFN gamma	0.0	0.0
B lymphocytes CD40L and IL-4	0.0	0.0	Dermal fibroblast CCD1070 rest	0.0	0.0
EOL-1 dbcAMP	0.0	0.0	Dermal fibroblast CCD1070 TNF alpha	0.0	0.0
EOL-1 dbcAMP PMA/ionomycin	0.0	0.0	Dermal fibroblast CCD1070 IL-1 beta	0.0	0.0

Dendritic cells none	0.0	0.0	Dermal fibroblast IFN gamma	0.0	0.0
Dendritic cells LPS	2.9	0.0	Dermal fibroblast IL-4	0.0	0.0
Dendritic cells anti-CD40	0.0	0.0	IBD Colitis 2	0.0	0.0
Monocytes rest	0.0	0.0	IBD Crohn's	0.0	0.0
Monocytes LPS	0.0	0.0	Colon	100.0	12.7
Macrophages rest	8.2	0.0	Lung	72.2	0.0
Macrophages LPS	0.0	0.0	Thymus	47.3	100.0
HUVEC none	0.0	0.0	Kidney	0.0	0.0
HUVEC starved	1.8	0.0			

CNS_neurodegeneration_v1.0 Summary: Ag2316 Data from this one run is not included due to a potential problem in one of the sample wells.

Panel 1.3D Summary: Ag2262/2316 The expression of this gene was assessed in 3 separate runs using two independent probe and primer sets with significant expression detected in spleen and fetal kidney in all runs. Thus, the expression of this gene could be used to distinguish spleen from other tissues in the panel. Moreover, the expression of this gene could also be used to distinguish fetal kidney tissue from adult kidney tissue.

Panel 2D Summary: Ag2262 The expression of this gene is highest in a sample derived from normal kidney tissue. Of note was the profound association of the expression of this gene with normal kidney tissue when compared to adjacent malignant tissue. Thus, the expression of this gene could be used to distinguish normal kidney tissue from malignant kidney tissue. Moreover, therapeutic modulation of the expression or function of this gene through the use of small molecule drugs, antibodies or protein therapeutics might be of benefit in the treatment of kidney cancer.

Panel 4D Summary: Ag2316 This transcript is expressed almost exclusively in the thymus (CT 33.2). Therefore, this transcript could be used for detection of thymic tissues.

Ag 2262 Using a second set of primers, expression of the NOV7 gene is also found in colon and lung, in addition to its expression in the thymus. Thus, this putative Wnt -15 protein may also play an important role in the normal homeostasis of these tissues. Therefore, therapeutics designed with the protein encoded by this transcript could be important for maintaining or restoring normal function to these organs during inflammation.

NOV8

Expression of gene NOV8 was assessed using the primer-probe set Ag2261, described in Table 60. Results of the RTQ-PCR runs are shown in Tables 61, 62 and 63.

Table 60. Probe Name Ag2261

Primers	Sequences	Length	Start Position	SEQ ID NO:
Forward	5'-ggatgactcgcttagcttct-3'	20	858	178
Probe	TET-5'-gccgtaggtgccaccgtgagaag-3'-TAMRA	23	911	179
Reverse	5'-agcagatgctctcgcagtt-3'	19	934	180

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Table 61. Panel 1.3D

Tissue Name	Rel. Exp.(%) Ag2261, Run 150631675	Rel. Exp.(%) Ag2261, Run 152887692	Tissue Name	Rel. Exp.(%) Ag2261, Run 150631675	Rel. Exp.(%) Ag2261, Run 152887692
Liver adenocarcinoma	22.4	19.6	Kidney (fetal)	2.1	0.0
Pancreas	3.9	2.5	Renal ca. 786-0	0.0	0.0
Pancreatic ca. CAPAN 2	5.3	3.5	Renal ca. A498	10.2	5.3
Adrenal gland	2.1	0.6	Renal ca. RXF 393	0.0	0.0
Thyroid	7.0	9.8	Renal ca. ACHN	0.0	2.2
Salivary gland	1.9	2.1	Renal ca. UO-31	0.0	0.0
Pituitary gland	1.0	2.2	Renal ca. TK-10	0.0	0.0
Brain (fetal)	6.8	4.9	Liver	0.0	0.0
Brain (whole)	4.8	3.0	Liver (fetal)	7.6	0.0
Brain (amygdala)	4.6	5.3	Liver ca. (hepatoblast) HepG2	0.0	0.0
Brain (cerebellum)	1.6	1.6	Lung	14.3	15.8
Brain (hippocampus)	7.5	11.3	Lung (fetal)	15.1	15.4
Brain (substantia nigra)	1.2	2.6	Lung ca. (small cell) LX-1	1.6	0.0
Brain (thalamus)	2.5	1.7	Lung ca. (small cell) NCI-H69	29.5	19.1
Cerebral Cortex	0.0	0.0	Lung ca. (s.cell var.) SHP-77	11.0	5.1
Spinal cord	1.7	2.1	Lung ca. (large cell) NCI-H460	0.0	0.0
glio/astro U87-MG	0.0	0.0	Lung ca. (non-sm. cell) A549	0.0	1.2
glio/astro U-118-	55.1	50.3	Lung ca. (non-	0.0	1.3

MG			s.cell) NCI-H23		
astrocytoma SW1783	0.0	7.5	Lung ca. (non-s.cell) HOP-62	0.0	1.7
neuro*; met SK-N-AS	0.0	0.0	Lung ca. (non-s.cl) NCI-H522	8.0	8.3
astrocytoma SF-539	1.9	4.7	Lung ca. (squam.) SW 900	4.0	0.0
astrocytoma SNB-75	2.0	4.9	Lung ca. (squam.) NCI-H596	15.8	10.2
glioma SNB-19	6.7	2.4	Mammary gland	7.2	4.1
glioma U251	2.1	4.5	Breast ca.* (pl.ef) MCF-7	1.7	3.4
glioma SF-295	10.0	0.6	Breast ca.* (pl.ef) MDA-MB-231	23.2	19.6
Heart (Fetal)	11.1	9.9	Breast ca.* (pl.ef) T47D	4.3	5.8
Heart	4.9	6.0	Breast ca. BT-549	0.0	4.2
Skeletal muscle (Fetal)	100.0	100.0	Breast ca. MDA-N	0.0	0.0
Skeletal muscle	5.5	8.4	Ovary	3.6	3.1
Bone marrow	0.0	0.0	Ovarian ca. OVCAR-3	1.1	1.0
Thymus	10.0	3.9	Ovarian ca. OVCAR-4	0.0	0.0
Spleen	3.8	4.2	Ovarian ca. OVCAR-5	0.0	0.0
Lymph node	5.0	1.1	Ovarian ca. OVCAR-8	1.3	4.3
Colorectal	3.4	5.4	Ovarian ca. IGROV-1	0.0	0.0
Stomach	6.0	15.4	Ovarian ca. (ascites) SK-OV-3	7.5	16.0
Small intestine	15.9	18.7	Uterus	17.8	15.1
Colon ca. SW480	24.3	15.3	Placenta	4.6	8.2
Colon ca.* SW620 (SW480 met)	0.0	0.0	Prostate	3.6	5.3
Colon ca. HT29	0.0	0.0	Prostate ca.* (bone met) PC-3	1.7	1.5
Colon ca. HCT-116	3.8	0.6	Testis	21.9	14.6
Colon ca. CaCo-2	0.0	0.8	Melanoma Hs688(A).T	3.1	4.7
CC Well to Mod	2.3	0.0	Melanoma*	0.4	1.3

Diff (ODO3866)			(met) Hs688(B).T		
Colon ca. HCC-2998	0.0	0.0	Melanoma UACC-62	0.0	0.0
Gastric ca. (liver met) NCI-N87	16.7	14.9	Melanoma M14	0.0	0.0
Bladder	1.6	3.2	Melanoma LOX IMVI	0.0	0.0
Trachea	24.3	33.7	Melanoma* (met) SK-MEL-5	0.0	2.0
Kidney	0.0	0.0	Adipose	6.7	7.2

Table 62. Panel 2D

Tissue Name	Rel. Exp.(%) Ag2261, Run 150811744	Rel. Exp.(%) Ag2261, Run 152887693	Tissue Name	Rel. Exp.(%) Ag2261, Run 150811744	Rel. Exp.(%) Ag2261, Run 152887693
Normal Colon	19.1	19.8	Kidney Margin 8120608	2.4	0.0
CC Well to Mod Diff (ODO3866)	0.0	5.8	Kidney Cancer 8120613	14.6	7.3
CC Margin (ODO3866)	19.5	12.5	Kidney Margin 8120614	4.8	1.5
CC Gr.2 rectosigmoid (ODO3868)	3.8	1.4	Kidney Cancer 9010320	0.0	0.0
CC Margin (ODO3868)	2.6	5.1	Kidney Margin 9010321	0.0	0.0
CC Mod Diff (ODO3920)	6.0	2.9	Normal Uterus	9.7	2.8
CC Margin (ODO3920)	23.8	6.4	Uterine Cancer 064011	85.9	41.5
CC Gr.2 ascend colon (ODO3921)	9.3	2.2	Normal Thyroid	15.2	7.3
CC Margin (ODO3921)	16.8	11.7	Thyroid Cancer	0.0	3.0
CC from Partial Hepatectomy (ODO4309) Mets	2.4	0.0	Thyroid Cancer A302152	1.9	1.2
Liver Margin (ODO4309)	2.6	0.0	Thyroid Margin A302153	2.6	2.8
Colon mets to lung (OD04451-01)	7.9	4.5	Normal Breast	16.2	2.7
Lung Margin (OD04451-02)	11.3	12.9	Breast Cancer	78.5	29.7
Normal Prostate 6546-1	6.3	2.6	Breast Cancer (OD04590-01)	37.6	23.8
Prostate Cancer (OD04410)	17.8	7.3	Breast Cancer Mets (OD04590-03)	100.0	24.5

Prostate Margin (OD04410)	10.7	7.4	Breast Cancer Metastasis	94.0	45.4
Prostate Cancer (OD04720-01)	4.7	4.4	Breast Cancer	25.7	24.8
Prostate Margin (OD04720-02)	13.9	5.6	Breast Cancer	23.2	7.1
Normal Lung	36.6	14.3	Breast Cancer 9100266	33.0	7.5
Lung Met to Muscle (ODO4286)	1.0	0.0	Breast Margin 9100265	7.6	7.6
Muscle Margin (ODO4286)	31.0	38.2	Breast Cancer A209073	13.9	0.9
Lung Malignant Cancer (OD03126)	81.8	100.0	Breast Margin A2090734	2.5	0.0
Lung Margin (OD03126)	35.8	18.2	Normal Liver	0.0	0.0
Lung Cancer (OD04404)	57.0	39.5	Liver Cancer	0.0	0.0
Lung Margin (OD04404)	9.4	11.8	Liver Cancer 1025	4.8	1.7
Lung Cancer (OD04565)	37.1	42.0	Liver Cancer 1026	7.1	0.0
Lung Margin (OD04565)	22.7	9.3	Liver Cancer 6004-T	4.8	0.0
Lung Cancer (OD04237-01)	5.3	6.4	Liver Tissue 6004-N	4.4	1.8
Lung Margin (OD04237-02)	78.5	32.8	Liver Cancer 6005-T	0.0	6.0
Ocular Mel Met to Liver (ODO4310)	0.0	0.0	Liver Tissue 6005-N	0.0	1.8
Liver Margin (ODO4310)	2.4	0.0	Normal Bladder	2.4	3.0
Melanoma Metastasis	13.0	0.0	Bladder Cancer	8.5	4.9
Lung Margin (OD04321)	96.6	50.0	Bladder Cancer	17.0	11.8
Normal Kidney	0.0	0.0	Bladder Cancer (OD04718-01)	10.0	5.7
Kidney Ca, Nuclear grade 2 (OD04338)	0.0	0.0	Bladder Normal Adjacent (OD04718-03)	19.3	27.5
Kidney Margin (OD04338)	4.0	4.6	Normal Ovary	13.6	12.4
Kidney Ca Nuclear grade 1/2 (OD04339)	0.0	3.3	Ovarian Cancer	37.9	2.1
Kidney Margin (OD04339)	18.7	0.0	Ovarian Cancer (OD04768-07)	18.4	3.7

Kidney Ca, Clear cell type (OD04340)	8.8	11.7	Ovary Margin (OD04768-08)	28.3	12.2
Kidney Margin (OD04340)	0.0	2.0	Normal Stomach	48.3	17.3
Kidney Ca, Nuclear grade 3 (OD04348)	3.5	4.0	Gastric Cancer 9060358	0.0	0.0
Kidney Margin (OD04348)	2.0	1.7	Stomach Margin 9060359	9.9	3.0
Kidney Cancer (OD04622-01)	9.3	0.0	Gastric Cancer 9060395	20.7	10.4
Kidney Margin (OD04622-03)	0.0	6.3	Stomach Margin 9060394	10.0	12.2
Kidney Cancer (OD04450-01)	0.0	0.0	Gastric Cancer 9060397	8.7	1.5
Kidney Margin (OD04450-03)	0.0	0.0	Stomach Margin 9060396	7.5	6.2
Kidney Cancer 8120607	0.0	0.7	Gastric Cancer 064005	10.7	4.8

Table 63. Panel 4D

Tissue Name	Rel. Exp.(%) Ag2261, Run 152887762	Tissue Name	Rel. Exp.(%) Ag2261, Run 152887762
Secondary Th1 act	0.0	HUVEC IL-1beta	0.0
Secondary Th2 act	0.0	HUVEC IFN gamma	3.7
Secondary Tr1 act	0.0	HUVEC TNF alpha + IFN gamma	0.0
Secondary Th1 rest	0.0	HUVEC TNF alpha + IL4	4.3
Secondary Th2 rest	0.0	HUVEC IL-11	4.0
Secondary Tr1 rest	0.0	Lung Microvascular EC none	7.2
Primary Th1 act	0.0	Lung Microvascular EC TNFalpha + IL-1beta	0.0
Primary Th2 act	0.0	Microvascular Dermal EC none	8.4
Primary Tr1 act	0.0	Microvascular Dermal EC TNFalpha + IL-1beta	0.0
Primary Th1 rest	0.0	Bronchial epithelium TNFalpha + IL1beta	0.0
Primary Th2 rest	0.0	Small airway epithelium none	5.9
Primary Tr1 rest	0.0	Small airway epithelium TNFalpha + IL-1beta	24.3
CD45RA CD4 lymphocyte act	0.0	Coronary artery SMC rest	0.0
CD45RO CD4	0.0	Coronary artery SMC	0.0

lymphocyte act		TNFalpha + IL-1beta	
CD8 lymphocyte act	0.0	Astrocytes rest	3.3
Secondary CD8 lymphocyte rest	0.0	Astrocytes TNFalpha + IL-1beta	0.0
Secondary CD8 lymphocyte act	1.6	KU-812 (Basophil) rest	0.0
CD4 lymphocyte none	0.0	KU-812 (Basophil) PMA/ionomycin	0.0
2ry Th1/Th2/Tr1_anti-CD95 CH11	0.0	CCD1106 (Keratinocytes) none	47.3
LAK cells rest	3.5	CCD1106 (Keratinocytes) TNFalpha + IL-1beta	9.0
LAK cells IL-2	0.0	Liver cirrhosis	32.8
LAK cells IL-2+IL-12	0.0	Lupus kidney	0.0
LAK cells IL-2+IFN gamma	0.0	NCI-H292 none	3.8
LAK cells IL-2+ IL-18	0.0	NCI-H292 IL-4	8.0
LAK cells PMA/ionomycin	26.1	NCI-H292 IL-9	0.0
NK Cells IL-2 rest	0.0	NCI-H292 IL-13	13.8
Two Way MLR 3 day	0.0	NCI-H292 IFN gamma	16.2
Two Way MLR 5 day	0.0	HPAEC none	6.7
Two Way MLR 7 day	0.0	HPAEC TNF alpha + IL-1 beta	0.0
PBMC rest	0.0	Lung fibroblast none	7.6
PBMC PWM	0.0	Lung fibroblast TNF alpha + IL-1 beta	3.1
PBMC PHA-L	0.0	Lung fibroblast IL-4	4.3
Ramos (B cell) none	0.0	Lung fibroblast IL-9	12.7
Ramos (B cell) ionomycin	0.0	Lung fibroblast IL-13	6.8
B lymphocytes PWM	0.0	Lung fibroblast IFN gamma	30.4
B lymphocytes CD40L and IL-4	3.1	Dermal fibroblast CCD1070 rest	0.0
EOL-1 dbcAMP	0.0	Dermal fibroblast CCD1070 TNF alpha	5.2
EOL-1 dbcAMP PMA/ionomycin	3.5	Dermal fibroblast CCD1070 IL-1 beta	0.0
Dendritic cells none	0.0	Dermal fibroblast IFN gamma	28.5
Dendritic cells LPS	0.0	Dermal fibroblast IL-4	42.9
Dendritic cells anti-CD40	0.0	IBD Colitis 2	2.2
Monocytes rest	0.0	IBD Crohn's	3.1
Monocytes LPS	0.0	Colon	100.0
Macrophages rest	0.0	Lung	36.3
Macrophages LPS	0.0	Thymus	0.0
HUVEC none	0.0	Kidney	4.0

HUVEC starved	17.4		
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Panel 1.3D Summary: Ag2261 The 88091010_EXT gene is expressed at moderate levels in a number of metabolic tissues, with highest overall expression seen in fetal skeletal muscle (CTs=30.4-31.8). The higher levels of expression in fetal skeletal muscle when compared to adult skeletal muscle suggest that the protein product encoded by the 88091010_EXT gene may be useful in treating muscular dystrophy, Lesch-Nyhan syndrome, myasthenia gravis and other conditions that result in weak or dystrophic muscle. This gene is also expressed in adipose, thyroid and heart. Since biologic cross-talk between adipose and thyroid is a component of some forms of obesity, this gene product may be a protein therapeutic for the treatment of metabolic disease, including obesity and Type 2 diabetes.

Panel 2D Summary: Ag2261 The expression of this gene was assessed in two independent runs on panel 2D. This gene is consistently expressed in samples of breast cancer, uterine cancer and lung cancer when compared to their respective normal adjacent tissue controls. Thus, the expression of this gene could be used to distinguish breast cancer, lung cancer or uterine cancer from their normal tissues. Moreover, therapeutic modulation of this gene, through the use of small molecule drugs, antibodies or protein therapeutics might be of use in the treatment of breast, lung or uterine cancer.

Panel 4D Summary: Ag 2261: This transcript is expressed at a low, but significant level in colon (CT 33.5). Low levels of expression of this transcript are also found in the lung, keratinocytes and dermal fibroblast. Thus, this transcript could be used as a marker for thymic, lung and skin tissues. The putative Wnt -14 encoded by this transcript may play an important role in the normal homeostasis of these tissues. Therefore, therapeutics designed with the protein encoded for by this transcript could be important for maintaining or restoring normal function to these organs during inflammation.

NOV9

Expression of NOV9 was assessed using the primer-probe set Ag2303, described in Table 64. Results of the RTQ-PCR runs are shown in Tables 65 and 66.

Table 64. Probe Name Ag2303

Primers	Sequences	Length	Start Position	SEQ ID NO:
Forward	5' - CATTGAGAGCGATAAGTTCACA - 3'	22	510	181
Probe	TET - 5' - AGAATGTGGAGCTCAACATCCACCTG - 3' - TAMRA	26	548	182

Reverse	5' -GATGCACGCTGAAGTCATTC-3'	20	579	183
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Table 65. Panel 1.3D

Tissue Name	Rel. Exp.(%) Ag2303, Run 167985232	Tissue Name	Rel. Exp.(%) Ag2303, Run 167985232
Liver adenocarcinoma	19.1	Kidney (fetal)	25.5
Pancreas	5.1	Renal ca. 786-0	7.4
Pancreatic ca. CAPAN 2	20.0	Renal ca. A498	6.8
Adrenal gland	2.7	Renal ca. RXF 393	15.5
Thyroid	2.3	Renal ca. ACHN	3.9
Salivary gland	7.2	Renal ca. UO-31	6.3
Pituitary gland	5.0	Renal ca. TK-10	16.4
Brain (fetal)	31.9	Liver	6.1
Brain (whole)	58.2	Liver (fetal)	6.7
Brain (amygdala)	33.9	Liver ca. (hepatoblast) HepG2	11.7
Brain (cerebellum)	55.5	Lung	14.7
Brain (hippocampus)	23.3	Lung (fetal)	11.0
Brain (substantia nigra)	15.3	Lung ca. (small cell) LX-1	36.6
Brain (thalamus)	21.9	Lung ca. (small cell) NCI-H69	15.0
Cerebral Cortex	80.1	Lung ca. (s.cell var.) SHP-77	60.7
Spinal cord	8.4	Lung ca. (large cell) NCI-H460	5.4
glio/astro U87-MG	12.0	Lung ca. (non-sm. cell) A549	14.3
glio/astro U-118-MG	10.8	Lung ca. (non-s.cell) NCI-H23	37.4
astrocytoma SW1783	15.5	Lung ca. (non-s.cell) HOP-62	14.5
neuro*; met SK-N-AS	7.0	Lung ca. (non-s.cl) NCI-H522	15.6
astrocytoma SF-539	9.9	Lung ca. (squam.) SW 900	16.2
astrocytoma SNB-75	15.9	Lung ca. (squam.) NCI-H596	33.2
glioma SNB-19	8.7	Mammary gland	17.6
glioma U251	20.7	Breast ca.* (pl.ef) MCF-7	17.1
glioma SF-295	7.9	Breast ca.* (pl.ef) MDA-MB-231	6.7
Heart (Fetal)	46.0	Breast ca.* (pl. ef) T47D	29.7
Heart	9.8	Breast ca. BT-549	4.0
Skeletal muscle (Fetal)	30.6	Breast ca. MDA-N	10.4
Skeletal muscle	26.6	Ovary	7.9
Bone marrow	29.5	Ovarian ca. OVCAR-3	13.3
Thymus	32.3	Ovarian ca. OVCAR-4	14.3
Spleen	26.4	Ovarian ca. OVCAR-5	62.4

Lymph node	26.2	Ovarian ca. OVCAR-8	3.9
Colorectal	11.0	Ovarian ca. IGROV-1	6.2
Stomach	7.9	Ovarian ca. (ascites) SK-OV-3	47.0
Small intestine	5.6	Uterus	5.0
Colon ca. SW480	15.6	Placenta	3.2
Colon ca.* SW620 (SW480 met)	100.0	Prostate	8.0
Colon ca. HT29	19.5	Prostate ca.* (bone met) PC-3	21.5
Colon ca. HCT-116	16.6	Testis	5.0
Colon ca. CaCo-2	21.9	Melanoma Hs688(A).T	4.3
CC Well to Mod Diff (ODO3866)	13.1	Melanoma* (met) Hs688(B).T	3.6
Colon ca. HCC-2998	33.9	Melanoma UACC-62	7.0
Gastric ca. (liver met) NCI-N87	18.8	Melanoma M14	5.0
Bladder	7.2	Melanoma LOX IMVI	13.3
Trachea	4.0	Melanoma* (met) SK-MEL-5	7.8
Kidney	7.6	Adipose	13.8

Table 66. Panel 4D

Tissue Name	Rel. Exp.(%) Ag2303, Run 151630338	Tissue Name	Rel. Exp.(%) Ag2303, Run 151630338
Secondary Th1 act	69.7	HUVEC IL-1beta	2.8
Secondary Th2 act	51.4	HUVEC IFN gamma	15.7
Secondary Tr1 act	66.0	HUVEC TNF alpha + IFN gamma	7.2
Secondary Th1 rest	24.5	HUVEC TNF alpha + IL4	7.2
Secondary Th2 rest	28.9	HUVEC IL-11	5.9
Secondary Tr1 rest	29.1	Lung Microvascular EC none	6.8
Primary Th1 act	53.2	Lung Microvascular EC TNFalpha + IL-1beta	5.4
Primary Th2 act	44.4	Microvascular Dermal EC none	10.1
Primary Tr1 act	66.0	Microvascular Dermal EC TNFalpha + IL-1beta	6.7
Primary Th1 rest	89.5	Bronchial epithelium TNFalpha + IL1beta	7.2
Primary Th2 rest	66.0	Small airway epithelium none	4.1
Primary Tr1 rest	46.7	Small airway epithelium TNFalpha + IL-1beta	20.4
CD45RA CD4 lymphocyte act	36.3	Coronary artery SMC rest	7.7
CD45RO CD4 lymphocyte act	55.5	Coronary artery SMC TNFalpha + IL-1beta	6.1

CD8 lymphocyte act	56.3	Astrocytes rest	4.4
Secondary CD8 lymphocyte rest	47.6	Astrocytes TNFalpha + IL-1beta	3.0
Secondary CD8 lymphocyte act	48.0	KU-812 (Basophil) rest	17.3
CD4 lymphocyte none	15.2	KU-812 (Basophil) PMA/ionomycin	31.2
2ry Th1/Th2/Tr1_anti-CD95 CH11	41.2	CCD1106 (Keratinocytes) none	11.8
LAK cells rest	34.4	CCD1106 (Keratinocytes) TNFalpha + IL-1beta	9.9
LAK cells IL-2	69.3	Liver cirrhosis	2.0
LAK cells IL-2+IL-12	55.9	Lupus kidney	2.1
LAK cells IL-2+IFN gamma	63.3	NCI-H292 none	21.0
LAK cells IL-2+ IL-18	57.0	NCI-H292 IL-4	33.2
LAK cells PMA/ionomycin	9.6	NCI-H292 IL-9	33.2
NK Cells IL-2 rest	47.6	NCI-H292 IL-13	20.9
Two Way MLR 3 day	38.7	NCI-H292 IFN gamma	25.0
Two Way MLR 5 day	39.5	HPAEC none	8.2
Two Way MLR 7 day	42.0	HPAEC TNF alpha + IL-1 beta	8.6
PBMC rest	21.5	Lung fibroblast none	5.9
PBMC PWM	100.0	Lung fibroblast TNF alpha + IL-1 beta	6.4
PBMC PHA-L	73.7	Lung fibroblast IL-4	12.2
Ramos (B cell) none	54.3	Lung fibroblast IL-9	9.9
Ramos (B cell) ionomycin	78.5	Lung fibroblast IL-13	9.6
B lymphocytes PWM	90.1	Lung fibroblast IFN gamma	11.6
B lymphocytes CD40L and IL-4	53.6	Dermal fibroblast CCD1070 rest	12.5
EOL-1 dbcAMP	57.4	Dermal fibroblast CCD1070 TNF alpha	67.8
EOL-1 dbcAMP PMA/ionomycin	18.8	Dermal fibroblast CCD1070 IL-1 beta	9.7
Dendritic cells none	22.1	Dermal fibroblast IFN gamma	5.5
Dendritic cells LPS	15.9	Dermal fibroblast IL-4	7.4
Dendritic cells anti-CD40	22.2	IBD Colitis 2	2.0
Monocytes rest	45.4	IBD Crohn's	1.4
Monocytes LPS	17.3	Colon	20.4
Macrophages rest	36.1	Lung	14.0
Macrophages LPS	18.0	Thymus	10.6
HUVEC none	13.7	Kidney	31.6
HUVEC starved	19.8		

Panel 1.3D Summary: Ag2303

NOV9 is widely expressed across the panel, with highest expression in a colon cancer cell line SW620 (CT=26.4). Of note is the difference in expression between the related colon cancer cell lines SW620 and SW480. SW480 represents the primary lesion from a patient with colon cancer, while SW620 represents a metastasis from the same patient. The difference in expression of this gene between the SW620 and SW480 cell lines indicates that it could be used to distinguish these cells, or others like them. Moreover, therapeutic modulation of NOV9, through the use of small molecule drugs, antibodies or protein therapeutics, may be effective in the treatment of metastatic colon cancer.

Among tissues with metabolic function, NOV9 is moderately expressed in the pancreas, adrenal, thyroid, pituitary, adipose, adult and fetal heart, and adult and fetal liver. This expression profile suggests that the NOV9 product may be an important small molecule target for the treatment of metabolic disease in any or all of these tissues, including obesity and diabetes.

NOV9, which encodes a beta-adrenergic receptor kinase, also shows high expression in all regions of the brain examined, especially in the cerebral cortex (CT=26.7) The beta adrenergic receptors have been shown to play a role in memory formation and in clinical depression. Since many current anti-depressants produce undesired side effects as a result of non-specific binding (to other receptors), this gene is therefore an excellent small molecule target for the treatment of clinical depression without side effects. Furthermore, the role of beta adrenergic receptors in memory consolidation suggests that the NOV9 gene product would also be useful as a small molecule target for the treatment of Alzheimer's disease, vascular dementia, or any memory loss disorder.

References:

1. Feighner JP. Mechanism of action of antidepressant medications. J Clin Psychiatry 1999;60 Suppl 4:4-11; discussion 12-3

The psychopharmacology of depression is a field that has evolved rapidly in just under 5 decades. Early antidepressant medications--tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs)--were discovered through astute clinical observations. These first-generation medications were effective because they enhanced serotonergic or noradrenergic mechanisms or both. Unfortunately, the TCAs also blocked histaminic, cholinergic, and alpha1-adrenergic receptor sites, and this action brought about unwanted side effects such as weight gain, dry mouth, constipation, drowsiness, and dizziness. MAOIs can interact with

tyramine to cause potentially lethal hypertension and present potentially dangerous interactions with a number of medications and over-the-counter drugs. The newest generation of antidepressants, including the single-receptor selective serotonin reuptake inhibitors (SSRIs) and multiple-receptor antidepressants venlafaxine, mirtazapine, bupropion, trazodone, and nefazodone, target one or more specific brain receptor sites without, in most cases, activating unwanted sites such as histamine and acetylcholine. This paper discusses the new antidepressants, particularly with regard to mechanism of action, and looks at future developments in the treatment of depression.

2. Ferry B, McGaugh JL. Role of amygdala norepinephrine in mediating stress hormone regulation of memory storage. *Acta Pharmacol Sin* 2000 Jun;21(6):481-93

There is extensive evidence indicating that the noradrenergic system of the amygdala, particularly the basolateral nucleus of the amygdala (BLA), is involved in memory consolidation. This article reviews the central hypothesis that stress hormones released during emotionally arousing experiences activate noradrenergic mechanisms in the BLA, resulting in enhanced memory for those events. Findings from experiments using rats have shown that the memory-modulatory effects of the adrenocortical stress hormones epinephrine and glucocorticoids involve activation of beta-adrenoceptors in the BLA. In addition, both behavioral and microdialysis studies have shown that the noradrenergic system of the BLA also mediates the influences of other neuromodulatory systems such as opioid peptidergic and GABAergic systems on memory storage. Other findings indicate that this stress hormone-induced activation of noradrenergic mechanisms in the BLA regulates memory storage in other brain regions.

Panel 4D Summary: Ag2303

NOV9, a beta-adrenergic receptor kinase homolog, is highly expressed (CTs 26-29) in a wide range of cells that play a significance role in the immune response. Highest expression of this gene is found in activated B and T cells. Therefore, inhibition of the function of the protein encoded by NOV9 with a small molecule drug may block the functions of B cells or T cells and could be beneficial in the treatment of patients suffering from autoimmune and inflammatory diseases such as asthma, allergies, inflammatory bowel disease, lupus erythematosus, or rheumatoid arthritis.

NOV10

Expression of NOV10 was assessed using the primer-probe set Ag2311, described in Table 67. Results of the RTQ-PCR runs are shown in Tables 68, 69, 70 and 71.

Table 67. Probe Name Ag2311

Primers	Sequences	Length	Start Position	SEQ ID NO:
Forward	5' - CTCTGGGGACTCCTAATTTCTG - 3'	22	2913	184
Probe	TET-5' - CCCAGCCTAAAGCAGGGATCAGTCTT-3' - TAMRA	26	2939	185
Reverse	5' - TCCAAGGATTTATTCCACAAGA - 3'	22	2966	186

Table 68. CNS_neurodegeneration_v1.0

Tissue Name	Rel. Exp.(%) Ag2311, Run 208253895	Tissue Name	Rel. Exp.(%) Ag2311, Run 208253895
AD 1 Hippo	33.4	Control (Path) 3 Temporal Ctx	13.4
AD 2 Hippo	46.3	Control (Path) 4 Temporal Ctx	44.8
AD 3 Hippo	12.9	AD 1 Occipital Ctx	36.1
AD 4 Hippo	15.4	AD 2 Occipital Ctx (Missing)	0.0
AD 5 Hippo	87.7	AD 3 Occipital Ctx	10.5
AD 6 Hippo	41.2	AD 4 Occipital Ctx	23.2
Control 2 Hippo	34.4	AD 5 Occipital Ctx	40.1
Control 4 Hippo	29.7	AD 5 Occipital Ctx	28.3
Control (Path) 3 Hippo	13.0	Control 1 Occipital Ctx	8.8
AD 1 Temporal Ctx	39.2	Control 2 Occipital Ctx	57.4
AD 2 Temporal Ctx	46.7	Control 3 Occipital Ctx	32.3
AD 3 Temporal Ctx	12.2	Control 4 Occipital Ctx	13.6
AD 4 Temporal Ctx	42.9	Control (Path) 1 Occipital Ctx	67.4
AD 5 Inf Temporal Ctx	100.0	Control (Path) 2 Occipital Ctx	26.8
AD 5 Sup Temporal Ctx	57.8	Control (Path) 3 Occipital Ctx	12.5
AD 6 Inf Temporal Ctx	48.3	Control (Path) 4 Occipital Ctx	36.6
AD 6 Sup Temporal Ctx	42.6	Control 1 Parietal Ctx	14.1
Control 1 Temporal Ctx	15.7	Control 2 Parietal Ctx	71.7
Control 2 Temporal Ctx	37.4	Control 3 Parietal Ctx	29.1
Control 3 Temporal Ctx	25.5	Control (Path) 1 Parietal Ctx	39.5
Control 3 Temporal Ctx	23.5	Control (Path) 2 Parietal Ctx	31.2
Control (Path) 1 Temporal Ctx	59.5	Control (Path) 3 Parietal Ctx	11.6
Control (Path) 2 Temporal Ctx	35.8	Control (Path) 4 Parietal Ctx	58.2

Table 69. Panel 1.3D

Tissue Name	Rel. Exp.(%) Ag2311, Run 165627680	Tissue Name	Rel. Exp.(%) Ag2311, Run 165627680
Liver adenocarcinoma	1.7	Kidney (fetal)	6.7
Pancreas	10.5	Renal ca. 786-0	1.3
Pancreatic ca. CAPAN 2	5.4	Renal ca. A498	6.5
Adrenal gland	22.2	Renal ca. RXF 393	3.3
Thyroid	21.5	Renal ca. ACHN	0.9
Salivary gland	10.6	Renal ca. UO-31	1.1
Pituitary gland	24.7	Renal ca. TK-10	1.3
Brain (fetal)	15.0	Liver	7.5
Brain (whole)	23.7	Liver (fetal)	10.8
Brain (amygdala)	24.7	Liver ca. (hepatoblast) HepG2	2.0
Brain (cerebellum)	24.5	Lung	27.5
Brain (hippocampus)	35.1	Lung (fetal)	7.5
Brain (substantia nigra)	100.0	Lung ca. (small cell) LX-1	4.6
Brain (thalamus)	27.7	Lung ca. (small cell) NCI-H69	0.0
Cerebral Cortex	9.9	Lung ca. (s.cell var.) SHP-77	5.4
Spinal cord	32.5	Lung ca. (large cell) NCI-H460	19.1
glio/astro U87-MG	4.2	Lung ca. (non-sm. cell) A549	3.2
glio/astro U-118-MG	9.2	Lung ca. (non-s.cell) NCI-H23	5.1
astrocytoma SW1783	3.7	Lung ca. (non-s.cell) HOP-62	3.5
neuro*; met SK-N-AS	12.2	Lung ca. (non-s.cl) NCI-H522	1.4
astrocytoma SF-539	4.1	Lung ca. (squam.) SW 900	1.9
astrocytoma SNB-75	3.7	Lung ca. (squam.) NCI-H596	0.3
glioma SNB-19	5.8	Mammary gland	18.0
glioma U251	28.9	Breast ca.* (pl.ef) MCF-7	6.1
glioma SF-295	4.5	Breast ca.* (pl.ef) MDA-MB-231	3.8
Heart (Fetal)	5.4	Breast ca.* (pl. ef) T47D	6.3
Heart	12.3	Breast ca. BT-549	1.0
Skeletal muscle (Fetal)	4.6	Breast ca. MDA-N	2.1
Skeletal muscle	22.8	Ovary	2.0
Bone marrow	15.1	Ovarian ca. OVCAR-3	4.3
Thymus	17.9	Ovarian ca. OVCAR-4	1.8
Spleen	21.9	Ovarian ca. OVCAR-5	9.8
Lymph node	27.7	Ovarian ca. OVCAR-8	1.0
Colorectal	3.0	Ovarian ca. IGROV-1	0.8
Stomach	12.9	Ovarian ca. (ascites) SK-OV-	2.8

		3	
Small intestine	66.4	Uterus	29.3
Colon ca. SW480	2.4	Placenta	8.2
Colon ca.* SW620 (SW480 met)	4.1	Prostate	28.7
Colon ca. HT29	2.4	Prostate ca.* (bone met) PC-3	1.7
Colon ca. HCT-116	2.7	Testis	38.7
Colon ca. CaCo-2	3.0	Melanoma Hs688(A).T	1.3
CC Well to Mod Diff (ODO3866)	5.8	Melanoma* (met) Hs688(B).T	2.0
Colon ca. HCC-2998	3.5	Melanoma UACC-62	2.9
Gastric ca. (liver met) NCI-N87	13.8	Melanoma M14	11.0
Bladder	4.5	Melanoma LOX IMVI	0.2
Trachea	13.1	Melanoma* (met) SK-MEL-5	2.9
Kidney	14.7	Adipose	9.7

Table 70. Panel 2.2

Tissue Name	Rel. Exp.(%) Ag2311, Run 174370590	Tissue Name	Rel. Exp.(%) Ag2311, Run 174370590
Normal Colon	9.4	Kidney Margin (OD04348)	100.0
Colon cancer (OD06064)	1.2	Kidney malignant cancer (OD06204B)	9.3
Colon Margin (OD06064)	0.6	Kidney normal adjacent tissue (OD06204E)	17.6
Colon cancer (OD06159)	1.5	Kidney Cancer (OD04450-01)	41.2
Colon Margin (OD06159)	5.5	Kidney Margin (OD04450-03)	14.9
Colon cancer (OD06297-04)	1.1	Kidney Cancer 8120613	2.9
Colon Margin (OD06297-015)	9.6	Kidney Margin 8120614	9.8
CC Gr.2 ascend colon (ODO3921)	9.8	Kidney Cancer 9010320	6.7
CC Margin (ODO3921)	3.6	Kidney Margin 9010321	5.4
Colon cancer metastasis (OD06104)	5.5	Kidney Cancer 8120607	6.3
Lung Margin (OD06104)	1.2	Kidney Margin 8120608	6.3
Colon mets to lung (OD04451-01)	22.2	Normal Uterus	17.6
Lung Margin (OD04451-02)	12.0	Uterine Cancer 064011	11.2
Normal Prostate	6.2	Normal Thyroid	3.3
Prostate Cancer (OD04410)	4.3	Thyroid Cancer	11.1
Prostate Margin (OD04410)	9.6	Thyroid Cancer A302152	33.4
Normal Ovary	17.3	Thyroid Margin A302153	9.7
Ovarian cancer (OD06283-03)	6.7	Normal Breast	28.7
Ovarian Margin (OD06283-07)	8.8	Breast Cancer	9.7

Ovarian Cancer	10.7	Breast Cancer	14.9
Ovarian cancer (OD06145)	4.2	Breast Cancer (OD04590-01)	32.5
Ovarian Margin (OD06145)	29.5	Breast Cancer Mets (OD04590-03)	12.2
Ovarian cancer (OD06455-03)	7.9	Breast Cancer Metastasis	25.5
Ovarian Margin (OD06455-07)	2.4	Breast Cancer	15.9
Normal Lung	26.2	Breast Cancer 9100266	1.8
Invasive poor diff. lung adeno (ODO4945-01)	8.3	Breast Margin 9100265	1.6
Lung Margin (ODO4945-03)	6.0	Breast Cancer A209073	2.1
Lung Malignant Cancer (OD03126)	16.0	Breast Margin A2090734	26.6
Lung Margin (OD03126)	5.5	Breast cancer (OD06083)	25.0
Lung Cancer (OD05014A)	7.0	Breast cancer node metastasis (OD06083)	27.5
Lung Margin (OD05014B)	7.3	Normal Liver	23.7
Lung cancer (OD06081)	20.4	Liver Cancer 1026	2.7
Lung Margin (OD06081)	12.3	Liver Cancer 1025	29.5
Lung Cancer (OD04237-01)	9.5	Liver Cancer 6004-T	24.0
Lung Margin (OD04237-02)	18.4	Liver Tissue 6004-N	23.2
Ocular Mel Met to Liver (ODO4310)	14.1	Liver Cancer 6005-T	9.0
Liver Margin (ODO4310)	15.0	Liver Tissue 6005-N	51.1
Melanoma Metastasis	12.5	Liver Cancer	31.4
Lung Margin (OD04321)	4.4	Normal Bladder	13.5
Normal Kidney	20.4	Bladder Cancer	6.4
Kidney Ca, Nuclear grade 2 (OD04338)	63.3	Bladder Cancer	11.3
Kidney Margin (OD04338)	11.5	Normal Stomach	48.6
Kidney Ca Nuclear grade 1/2 (OD04339)	46.3	Gastric Cancer 9060397	5.6
Kidney Margin (OD04339)	17.4	Stomach Margin 9060396	4.0
Kidney Ca, Clear cell type (OD04340)	24.8	Gastric Cancer 9060395	4.0
Kidney Margin (OD04340)	17.0	Stomach Margin 9060394	9.1
Kidney Ca, Nuclear grade 3 (OD04348)	3.1	Gastric Cancer 064005	7.9

Table 71. Panel 4D

Tissue Name	Rel. Exp.(%) Ag2311, Run 158928074	Tissue Name	Rel. Exp.(%) Ag2311, Run 158928074
Secondary Th1 act	29.3	HUVEC IL-1beta	6.1
Secondary Th2 act	33.2	HUVEC IFN gamma	37.6

Secondary Tr1 act	45.7	HUVEC TNF alpha + IFN gamma	36.3
Secondary Th1 rest	17.3	HUVEC TNF alpha + IL4	34.9
Secondary Th2 rest	19.2	HUVEC IL-11	17.8
Secondary Tr1 rest	27.7	Lung Microvascular EC none	30.4
Primary Th1 act	36.9	Lung Microvascular EC TNFalpha + IL-1beta	43.8
Primary Th2 act	36.9	Microvascular Dermal EC none	39.5
Primary Tr1 act	45.7	Microsvascular Dermal EC TNFalpha + IL-1beta	27.4
Primary Th1 rest	38.7	Bronchial epithelium TNFalpha + IL1beta	1.2
Primary Th2 rest	27.0	Small airway epithelium none	6.2
Primary Tr1 rest	37.6	Small airway epithelium TNFalpha + IL-1beta	20.0
CD45RA CD4 lymphocyte act	17.2	Coronary artery SMC rest	9.5
CD45RO CD4 lymphocyte act	24.0	Coronary artery SMC TNFalpha + IL-1beta	7.7
CD8 lymphocyte act	21.9	Astrocytes rest	10.9
Secondary CD8 lymphocyte rest	26.2	Astrocytes TNFalpha + IL-1beta	9.9
Secondary CD8 lymphocyte act	17.4	KU-812 (Basophil) rest	40.1
CD4 lymphocyte none	5.9	KU-812 (Basophil) PMA/ionomycin	52.9
2ry Th1/Th2/Tr1_anti-CD95 CH11	19.8	CCD1106 (Keratinocytes) none	9.6
LAK cells rest	32.8	CCD1106 (Keratinocytes) TNFalpha + IL-1beta	0.6
LAK cells IL-2	23.3	Liver cirrhosis	10.8
LAK cells IL-2+IL-12	31.0	Lupus kidney	6.9
LAK cells IL-2+IFN gamma	27.5	NCI-H292 none	65.1
LAK cells IL-2+ IL-18	38.7	NCI-H292 IL-4	65.1
LAK cells PMA/ionomycin	17.4	NCI-H292 IL-9	71.7
NK Cells IL-2 rest	28.5	NCI-H292 IL-13	41.2
Two Way MLR 3 day	36.9	NCI-H292 IFN gamma	43.8
Two Way MLR 5 day	19.5	HPAEC none	30.8
Two Way MLR 7 day	16.4	HPAEC TNF alpha + IL-1 beta	16.8
PBMC rest	23.5	Lung fibroblast none	25.7
PBMC PWM	35.1	Lung fibroblast TNF alpha + IL-1 beta	9.0
PBMC PHA-L	17.8	Lung fibroblast IL-4	43.5
Ramos (B cell) none	21.8	Lung fibroblast IL-9	27.4

Ramos (B cell) ionomycin	37.4	Lung fibroblast IL-13	29.1
B lymphocytes PWM	72.7	Lung fibroblast IFN gamma	23.5
B lymphocytes CD40L and IL-4	66.0	Dermal fibroblast CCD1070 rest	42.3
EOL-1 dbcAMP	35.8	Dermal fibroblast CCD1070 TNF alpha	62.9
EOL-1 dbcAMP PMA/ionomycin	38.4	Dermal fibroblast CCD1070 IL-1 beta	28.3
Dendritic cells none	59.0	Dermal fibroblast IFN gamma	18.3
Dendritic cells LPS	32.5	Dermal fibroblast IL-4	33.2
Dendritic cells anti-CD40	33.4	IBD Colitis 2	5.3
Monocytes rest	42.9	IBD Crohn's	5.2
Monocytes LPS	25.0	Colon	27.5
Macrophages rest	42.3	Lung	14.5
Macrophages LPS	18.7	Thymus	47.6
HUVEC none	37.9	Kidney	100.0
HUVEC starved	40.1		

CNS_neurodegeneration_v1.0 Summary: Ag2311

NOV10 does not show differential expression between Alzheimer's diseased brains and control brains. However, this panel confirms the expression of this gene in the brains of an independent group of patients. Please see panel 1.3d for discussion of utility in the central nervous system.

Panel 1.3D Summary: Ag2311

NOV10, an alpha mannosidase isoform, is expressed at moderate levels in all regions of the brain examined, with highest expression in the substantia nigra (CT=29.3). In the brain, alpha mannosidase has been implicated in the processes of myelination and axon growth.

Therefore, therapeutic modulation of this gene or its protein product may be of use in the treatment of disorders where myelination has been compromised such as multiple sclerosis, and schizophrenia. In addition, the protein encoded by NOV10 could be useful in clinical situations where increased axonal growth is desired including spinal cord or brain trauma, stroke, or peripheral nerve injury.

NOV10 gene is moderately expressed (CT values = 31-34) in a variety of metabolic tissues including pancreas, adrenal, thyroid, pituitary, adult and fetal heart, adult and fetal liver, adult and fetal skeletal muscle, and adipose. This expression profile suggests that the protein encoded by the NOV10 may be an important small molecule target for the treatment of metabolic disease in any or all of these tissues, including obesity and diabetes.

The expression of this gene appears to be generally associated with normal tissues when compared to cell lines. Of note was the difference in expression in normal prostate when compared to the prostate cancer cell line (PC-3). Thus, NOV10 could be used to distinguish this sample on the panel from other samples or to distinguish normal prostate from prostate cancer. Moreover, therapeutic modulation of this gene, through the use of small molecule drugs, antibodies or protein therapeutics, might be of use in the treatment of prostate cancer.

References:

1. Vite CH, McGowan JC, Braund KG, Drobatz KJ, Glickson JD, Wolfe JH, Haskins ME. Histopathology, electrodiagnostic testing, and magnetic resonance imaging show significant peripheral and central nervous system myelin abnormalities in the cat model of alpha-mannosidosis. *J Neuropathol Exp Neurol* 2001 Aug;60(8):817-28

Alpha-mannosidosis is a disease caused by the deficient activity of alpha-mannosidase, a lysosomal hydrolase involved in the degradation of glycoproteins. The disease is characterized by the accumulation of mannose-rich oligosaccharides within lysosomes. The purpose of this study was to characterize the peripheral nervous system (PNS) and central nervous system (CNS) myelin abnormalities in cats from a breeding colony with a uniform mutation in the gene encoding alpha-mannosidase. Three affected cats and 3 normal cats from 2 litters were examined weekly from 4 to 18 wk of age. Progressively worsening neurological signs developed in affected cats that included tremors, loss of balance, and nystagmus. In the PNS, affected cats showed slow motor nerve conduction velocity and increased F-wave latency. Single nerve fiber teasing revealed significant demyelination/remyelination in affected cats. Mean G-ratios of nerves showed a significant increase in affected cats compared to normal cats. Magnetic resonance imaging of the CNS revealed diffuse white matter signal abnormalities throughout the brain of affected cats. Quantitative magnetization transfer imaging showed a 8%-16% decrease in the magnetization transfer ratio in brain white matter of affected cats compared to normal cats, consistent with myelin abnormalities. Histology confirmed myelin loss throughout the cerebrum and cerebellum. Thus, histology, electrodiagnostic testing, and magnetic resonance imaging identified significant myelination abnormalities in both the PNS and CNS that have not been described previously in alpha-mannosidosis.

2. Zmuda JF, Rivas RJ. The Golgi apparatus and the centrosome are localized to the sites of newly emerging axons in cerebellar granule neurons in vitro. *Cell Motil Cytoskeleton* 1998;41(1):18-38

Cultured cerebellar granule neurons develop their characteristic axonal and dendritic morphologies in a series of discrete temporal steps highly similar to those observed in situ, initially extending a single process, followed by the extension of a second process from the opposite pole of the cell, both of which develop into axons to generate a bipolar morphology.

5 A mature morphology is attained following the outgrowth of multiple, short dendrites [Powell et al., 1997: J. Neurobiol. 32:223-236]. To determine the relationship between the localization of the Golgi apparatus, the site of microtubule nucleation (the centrosome), and the sites of initial and secondary axonal extension, the intracellular positioning of the Golgi and centrosome was observed during the differentiation of postnatal mouse granule neurons in

10 vitro. The Golgi was labeled using the fluorescent lipid analogue, C5-DMB-Ceramide, or by indirect immunofluorescence using antibodies against the Golgi resident protein, alpha-mannosidase II. At 1-2 days in vitro (DIV), the Golgi was positioned at the base of the initial process in 99% of unipolar cells observed. By 3 DIV, many cells began the transition to a bipolar morphology by extending a short neurite from the pole of the cell opposite to the initial

15 process. The Golgi was observed at this site of secondary outgrowth in 92% of these "transitional" cells, suggesting that the Golgi was repositioned from the base of the initial process to the site of secondary neurite outgrowth. As the second process elongated and the cells proceeded to the bipolar stage of development, or at later stages when distinct axonal and somatodendritic domains had been established, the Golgi was not consistently positioned at

20 the base of either axons or dendrites, and was most often found at sites on the plasma membrane from which no processes originated. To determine the location of the centrosome in relation to the Golgi during development, granule neurons were labeled with antibodies against gamma-tubulin and optically sectioned using confocal microscopy. The centrosome was consistently co-localized with the Golgi during all stages of differentiation, and also

25 appeared to be repositioned to the base of the newly emerging axon during the transition from a unipolar to a bipolar morphology. These findings indicate that during the early stages of granule cell axonal outgrowth, the Golgi-centrosome is positioned at the base of the initial axon and is then repositioned to the base of the newly emerging secondary axon. Such an intracellular reorientation of these organelles may be important in maintaining the

30 characteristic developmental pattern of granule neurons by establishing the polarized microtubule network and the directed flow of membranous vesicles required for initial axonal elaboration

Panel 2.2 Summary: Ag2311

The expression of this gene is highest in a sample derived from normal kidney tissue adjacent to a kidney cancer. Furthermore, there appears to be substantial expression in normal stomach, normal liver adjacent to a cancer, normal breast adjacent to a cancer and normal ovary adjacent to a cancer. Thus, the expression of this gene could be used to distinguish these normal tissues from their malignant counterparts. Moreover, therapeutic modulation of this gene, through the use of small molecule drugs, antibodies or protein therapeutics might be of use in the treatment of kidney, liver, breast or ovarian cancer.

Panel 4D Summary: Ag2311

NOV10 is modestly expressed (CT values = 30-33) in a wide variety of immune cell types and tissues. The highest expression of this gene is found in B cells stimulated with PWM and anti-CD40, where stimulation normally leads to the production of immunoglobulin (Ig) and Ig switching. High levels of expression of this transcript are also found in a pulmonary muco-epidermoid cell line (H292) treated with Th2 cytokines. These findings suggest that the NOV10 product may be important in the pathogenesis, and/or treatment of autoimmune diseases such as lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, allergies which are associated with hyper IgE production, and lung inflammatory diseases such as asthma and emphysema. In addition, the high expression of this gene in the kidney suggests that the protein encoded by this transcript may be involved in normal tissue/cellular functions particularly in the kidney.

NOV11a, NOV11b

Expression of NOV11a and NOV11b was assessed using the primer-probe set Ag3670, described in Table 72. Results of the RTQ-PCR runs are shown in Tables 73 and 74.

Table 72. Probe Name Ag3670

Primers	Sequences	Length	Start Position	SEQ ID NO:
Forward	5' - ACGAGGTCTTCATCAAGCTG - 3'	20	705	187
Probe	TET- 5' - CACCAACAAGTACAGCACCTTCTCCG - 3' - TAMRA	26	751	188
Reverse	5' - CAGTCGGGGTAGATGATGAA - 3'	20	779	189

Table 73. General_screening_panel_v1.4

Tissue Name	Rel. Exp.(%) Ag3670.	Rel. Exp.(%) Ag3670.	Tissue Name	Rel. Exp.(%) Ag3670.	Rel. Exp.(%) Ag3670.

	Run 216517130	Run 222735036		Run 216517130	Run 222735036
Adipose	0.2	0.4	Renal ca. TK-10	2.1	1.1
Melanoma* Hs688(A).T	0.0	0.0	Bladder	0.4	0.0
Melanoma* Hs688(B).T	0.0	0.0	Gastric ca. (liver met.) NCI-N87	0.8	0.4
Melanoma* M14	6.0	6.9	Gastric ca. KATO III	0.4	0.4
Melanoma* LOXIMVI	2.6	1.8	Colon ca. SW-948	0.0	0.1
Melanoma* SK- MEL-5	5.9	8.2	Colon ca. SW480	2.6	3.5
Squamous cell carcinoma SCC-4	0.2	0.0	Colon ca.* (SW480 met) SW620	1.3	0.8
Testis Pool	3.2	1.5	Colon ca. HT29	0.1	0.0
Prostate ca.* (bone met) PC-3	11.0	11.7	Colon ca. HCT-116	27.0	25.9
Prostate Pool	0.0	0.1	Colon ca. CaCo-2	11.7	13.3
Placenta	0.0	0.0	Colon cancer tissue	0.0	0.3
Uterus Pool	0.1	0.1	Colon ca. SW1116	12.9	7.2
Ovarian ca. OVCAR-3	2.3	1.2	Colon ca. Colo-205	0.4	0.2
Ovarian ca. SK-OV- 3	1.9	3.2	Colon ca. SW-48	0.0	0.3
Ovarian ca. OVCAR-4	1.5	1.5	Colon Pool	0.0	0.4
Ovarian ca. OVCAR-5	6.3	6.0	Small Intestine Pool	0.0	0.0
Ovarian ca. IGROV- 1	0.6	1.6	Stomach Pool	0.1	0.2
Ovarian ca. OVCAR-8	6.9	7.9	Bone Marrow Pool	0.2	0.1
Ovary	0.0	0.0	Fetal Heart	0.0	0.0
Breast ca. MCF-7	1.5	2.7	Heart Pool	0.0	0.0
Breast ca. MDA- MB-231	0.8	0.6	Lymph Node Pool	0.2	0.2
Breast ca. BT 549	6.8	11.6	Fetal Skeletal Muscle	0.0	0.0
Breast ca. T47D	21.8	16.8	Skeletal Muscle Pool	0.0	0.0
Breast ca. MDA-N	4.0	2.8	Spleen Pool	0.0	0.0
Breast Pool	0.0	0.0	Thymus Pool	0.3	0.1
Trachea	0.0	0.3	CNS cancer (glio/astro) U87-MG	0.5	1.2
Lung	0.0	0.0	CNS cancer (glio/astro) U-118-MG	3.2	3.2
Fetal Lung	0.0	0.0	CNS cancer	6.4	10.0

			(neuro;met) SK-N-AS		
Lung ca. NCI-N417	5.7	4.5	CNS cancer (astro) SF-539	2.6	0.8
Lung ca. LX-1	0.2	0.5	CNS cancer (astro) SNB-75	0.9	1.6
Lung ca. NCI-H146	0.5	0.8	CNS cancer (glio) SNB-19	0.3	0.8
Lung ca. SHP-77	0.6	2.7	CNS cancer (glio) SF-295	4.9	4.4
Lung ca. A549	6.8	6.6	Brain (Amygdala) Pool	0.0	0.3
Lung ca. NCI-H526	1.6	2.5	Brain (cerebellum)	0.0	0.3
Lung ca. NCI-H23	16.4	12.7	Brain (fetal)	2.0	2.7
Lung ca. NCI-H460	0.3	0.0	Brain (Hippocampus) Pool	0.3	0.8
Lung ca. HOP-62	0.6	0.8	Cerebral Cortex Pool	0.0	0.2
Lung ca. NCI-H522	48.6	46.0	Brain (Substantia nigra) Pool	0.4	0.7
Liver	0.0	0.0	Brain (Thalamus) Pool	0.4	0.9
Fetal Liver	0.0	0.0	Brain (whole)	0.1	0.1
Liver ca. HepG2	0.1	0.3	Spinal Cord Pool	0.2	0.3
Kidney Pool	0.1	0.0	Adrenal Gland	0.0	0.0
Fetal Kidney	1.0	1.9	Pituitary gland Pool	0.0	0.3
Renal ca. 786-0	100.0	100.0	Salivary Gland	0.0	0.2
Renal ca. A498	10.2	21.3	Thyroid (female)	1.2	0.3
Renal ca. ACHN	0.5	0.2	Pancreatic ca. CAPAN2	0.9	0.2
Renal ca. UO-31	1.5	1.8	Pancreas Pool	0.0	0.2

Table 74. Panel 4.1D

Tissue Name	Rel. Exp.(%) Ag3670, Run 223785547	Tissue Name	Rel. Exp.(%) Ag3670, Run 223785547
Secondary Th1 act	0.0	HUVEC IL-1beta	27.5
Secondary Th2 act	0.0	HUVEC IFN gamma	29.9
Secondary Tr1 act	0.0	HUVEC TNF alpha + IFN gamma	19.5
Secondary Th1 rest	0.0	HUVEC TNF alpha + IL4	0.0
Secondary Th2 rest	0.0	HUVEC IL-11	0.0
Secondary Tr1 rest	0.0	Lung Microvascular EC none	0.0
Primary Th1 act	0.0	Lung Microvascular EC TNFalpha + IL-1beta	11.6
Primary Th2 act	0.0	Microvascular Dermal EC none	0.0

Primary Tr1 act	0.0	Microsvascular Dermal EC TNFalpha + IL-1beta	71.7
Primary Th1 rest	0.0	Bronchial epithelium TNFalpha + IL1beta	53.2
Primary Th2 rest	0.0	Small airway epithelium none	0.0
Primary Tr1 rest	0.0	Small airway epithelium TNFalpha + IL-1beta	0.0
CD45RA CD4 lymphocyte act	0.0	Coronary artery SMC rest	0.0
CD45RO CD4 lymphocyte act	0.0	Coronary artery SMC TNFalpha + IL-1beta	0.0
CD8 lymphocyte act	15.1	Astrocytes rest	0.0
Secondary CD8 lymphocyte rest	0.0	Astrocytes TNFalpha + IL-1beta	0.0
Secondary CD8 lymphocyte act	39.5	KU-812 (Basophil) rest	0.0
CD4 lymphocyte none	0.0	KU-812 (Basophil) PMA/ionomycin	0.0
2ry Th1/Th2/Tr1_anti-CD95 CH11	0.0	CCD1106 (Keratinocytes) none	0.0
LAK cells rest	0.0	CCD1106 (Keratinocytes) TNFalpha + IL-1beta	38.2
LAK cells IL-2	0.0	Liver cirrhosis	0.0
LAK cells IL-2+IL-12	0.0	NCI-H292 none	0.0
LAK cells IL-2+IFN gamma	0.0	NCI-H292 IL-4	34.9
LAK cells IL-2+ IL-18	0.0	NCI-H292 IL-9	24.8
LAK cells PMA/ionomycin	0.0	NCI-H292 IL-13	21.5
NK Cells IL-2 rest	0.0	NCI-H292 IFN gamma	33.9
Two Way MLR 3 day	0.0	HPAEC none	0.0
Two Way MLR 5 day	0.0	HPAEC TNF alpha + IL-1 beta	0.0
Two Way MLR 7 day	0.0	Lung fibroblast none	12.8
PBMC rest	0.0	Lung fibroblast TNF alpha + IL-1 beta	0.0
PBMC PWM	0.0	Lung fibroblast IL-4	29.3
PBMC PHA-L	0.0	Lung fibroblast IL-9	46.7
Ramos (B cell) none	0.0	Lung fibroblast IL-13	0.0
Ramos (B cell) ionomycin	0.0	Lung fibroblast IFN gamma	0.0
B lymphocytes PWM	0.0	Dermal fibroblast CCD1070 rest	24.5
B lymphocytes CD40L and IL-4	0.0	Dermal fibroblast CCD1070 TNF alpha	22.8
EOL-1 dbcAMP	100.0	Dermal fibroblast CCD1070 IL-1 beta	0.0
EOL-1 dbcAMP PMA/ionomycin	45.1	Dermal fibroblast IFN gamma	0.0
Dendritic cells none	0.0	Dermal fibroblast IL-4	0.0
Dendritic cells LPS	0.0	Dermal Fibroblasts rest	0.0
Dendritic cells anti-CD40	0.0	Neutrophils TNFa+LPS	0.0

Monocytes rest	0.0	Neutrophils rest	0.0
Monocytes LPS	0.0	Colon	0.0
Macrophages rest	0.0	Lung	0.0
Macrophages LPS	0.0	Thymus	0.0
HUVEC none	25.9	Kidney	59.5
HUVEC starved	0.0		

General_screening_panel_v1.4 Summary: Ag3670

Two experiments with the same probe and primer sets show results that are in excellent agreement, with highest expression in a renal cancer cell line. In general, the expression of this gene appears to be largely associated with samples derived from cancer cell lines rather than normal tissues. Of note is the substantial expression associated with kidney cancer cell lines as well as in colon cancer and lung cancer cell lines. Thus, the expression of this gene could be used to distinguish these cell lines from other cell lines. Moreover, therapeutic modulation of this gene, through the use of small molecule drugs, antibodies or protein therapeutics might be of use in the treatment of kidney, colon or lung cancer.

This gene is a C1q-related factor variant, and is expressed in at least the fetal brain, hippocampus, substantia nigra and thalamus. Various members of the complement cascade have been implicated in neuroinflammation and the pathology of Alzheimer's disease. Recent case controlled studies also suggest that the use of anti-inflammatory agents decreases the risk of Alzheimer's disease. Therefore, this gene is an excellent drug target for the disruption of neuroinflammation and the treatment of Alzheimer's disease, Huntington's disease, and stroke.

References:

Lue LF, Rydel R, Brigham EF, Yang LB, Hampel H, Murphy GM Jr, Brachova L, Yan SD, Walker DG, Shen Y, Rogers J. Inflammatory repertoire of Alzheimer's disease and nondemented elderly microglia in vitro. *Glia* 2001 Jul;35(1):72-9

In this study complement activation and biosynthesis have been analysed in the brains of Huntington's disease (HD) (n = 9) and normal (n = 3) individuals. In HD striatum, neurons, myelin and astrocytes were strongly stained with antibodies to C1q, C4, C3, iC3b-neoepitope and C9-neoepitope. In contrast, no staining for complement components was found in the normal striatum. Marked astrogliosis and microgliosis were observed in all HD caudate and the internal capsule samples but not in normal brain. RT-PCR analysis and in-situ hybridisation were carried out to determine whether complement was synthesised locally by activated glial cells. By RT-PCR, we found that complement activators of the classical

pathway C1q C chain, C1r, C4, C3, as well as the complement regulators, C1 inhibitor, clusterin, MCP, DAF, CD59, were all expressed constitutively and at much higher level in HD brains compared to normal brain. Complement anaphylatoxin receptor mRNAs (C5a receptor and C3a receptor) were strongly expressed in HD caudate. In general, we found that the level
5 of complement mRNA in normal control brains was from 2 to 5 fold lower compared to HD striatum. Using in-situ hybridisation, we confirmed that C3 mRNA and C9 mRNA were expressed by reactive microglia in HD internal capsule. We propose that complement produced locally by reactive microglia is activated on the membranes of neurons, contributing to neuronal necrosis but also to proinflammatory activities. Complement opsonins (iC3b) and
10 anaphylatoxins (C3a, C5a) may be involved in the recruitment and stimulation of glial cells and phagocytes bearing specific complement receptors.

Panel 4.1D Summary: Ag3670

The NOV11 transcript, which encodes a protein with homology to a C1q related factor, is expressed at a low level in eosinophils, microvascular dermal endothelial cells and bronchial
15 epithelium. The inflammatory cytokines TNF- α and IL-1 β appear to up-regulate expression of this transcript in the endothelial cells and bronchial epithelium. This suggests that expression of this transcript is regulated by inflammatory conditions such as those found in lung inflammatory disease including pneumonia and bronchitis as well as skin infection or wounds. Expression of this transcript is also up regulated in lung fibroblasts by the Th2 cytokines IL9
20 or IL4, conditions found in asthma and COPD. The expression of this transcript in eosinophils, cells that are frequently associated with asthma, ulcerative colitis or other Th2 mediated diseases strongly suggest that modulation of the expression of this transcript will be beneficial in the treatment of atopic lung and skin diseases. Since the C1q factor is usually involved in the activation of complement and innate immunity, modulation of the expression of this
25 transcript could modulate excessive inflammatory processes leading to these diseases.

Panel 5D Summary: Expression is low/undetectable for all samples in this panel (CT>35). (Data not shown).

NOV12

Expression of NOV12 was assessed using the primer-probe sets Ag1586 and Ag2011,
30 described in Tables 75 and 76. Results of the RTQ-PCR runs are shown in Tables 77, 78, 79 and 80.

Table 75. Probe Name Ag1586

Primers	Sequences	Length	Start Position	SEQ ID NO:
Forward	5' - ACCAGGATGAGTTTGTGTCATC - 3'	22	735	190
Probe	TET - 5' - CTCAAGATCCCTTCGGACACGCTGT - 3' - TAMRA	25	761	191
Reverse	5' - TCGGAAGCTGTACACATAGTA - 3'	22	809	192

Table 76. Probe Name Ag2011

Primers	Sequences	Length	Start Position	SEQ ID NO:
Forward	5' - ACCAGGATGAGTTTGTGTCATC - 3'	22	735	193
Probe	TET - 5' - CTCAAGATCCCTTCGGACACGCTGT - 3' - TAMRA	25	761	194
Reverse	5' - TCGGAAGCTGTACACATAGTA - 3'	22	809	195

Table 77. Panel 1.3D

Tissue Name	Rel. Exp.(%) Ag1586, Run 146473155	Rel. Exp.(%) Ag2011, Run 147816085	Tissue Name	Rel. Exp.(%) Ag1586, Run 146473155	Rel. Exp.(%) Ag2011, Run 147816085
Liver adenocarcinoma	29.9	37.6	Kidney (fetal)	3.8	3.7
Pancreas	1.7	0.7	Renal ca. 786-0	6.1	11.7
Pancreatic ca. CAPAN 2	6.3	9.6	Renal ca. A498	25.0	25.9
Adrenal gland	2.6	2.5	Renal ca. RXF 393	4.5	5.0
Thyroid	2.5	1.8	Renal ca. ACHN	8.8	11.3
Salivary gland	1.9	2.2	Renal ca. UO-31	15.0	15.0
Pituitary gland	0.9	1.5	Renal ca. TK-10	4.4	4.6
Brain (fetal)	12.2	13.1	Liver	0.2	0.1
Brain (whole)	9.7	10.7	Liver (fetal)	0.7	0.8
Brain (amygdala)	9.5	9.9	Liver ca. (hepatoblast) HepG2	16.8	12.8
Brain (cerebellum)	3.3	2.3	Lung	5.0	5.1
Brain (hippocampus)	24.7	21.0	Lung (fetal)	7.4	8.1
Brain (substantia nigra)	0.9	1.3	Lung ca. (small cell) LX-1	16.8	12.1
Brain (thalamus)	4.7	3.7	Lung ca. (small cell) NCI-H69	18.4	23.7
Cerebral Cortex	75.8	71.2	Lung ca. (s.cell var.) SHP-77	8.5	7.2
Spinal cord	2.0	2.4	Lung ca. (large	10.7	10.1

			cell)NCI-H460		
glio/astro U87-MG	15.3	17.9	Lung ca. (non-sm. cell) A549	3.2	4.1
glio/astro U-118-MG	38.2	41.2	Lung ca. (non-s.cell) NCI-H23	23.2	24.7
astrocytoma SW1783	8.3	10.4	Lung ca. (non-s.cell) HOP-62	18.9	15.7
neuro*; met SK-N-AS	23.5	24.3	Lung ca. (non-s.cl) NCI-H522	5.6	7.5
astrocytoma SF-539	19.6	38.4	Lung ca. (squam.) SW 900	13.0	13.1
astrocytoma SNB-75	44.4	45.1	Lung ca. (squam.) NCI-H596	6.5	5.7
glioma SNB-19	26.2	12.2	Mammary gland	11.5	9.3
glioma U251	16.4	16.2	Breast ca.* (pl.ef) MCF-7	14.1	14.4
glioma SF-295	26.4	36.9	Breast ca.* (pl.ef) MDA-MB-231	82.9	87.1
Heart (Fetal)	80.7	95.3	Breast ca.* (pl. ef) T47D	6.1	4.6
Heart	2.8	1.9	Breast ca. BT-549	13.6	11.2
Skeletal muscle (Fetal)	85.3	87.7	Breast ca. MDA-N	28.1	31.6
Skeletal muscle	2.1	2.4	Ovary	20.9	19.5
Bone marrow	0.6	0.3	Ovarian ca. OVCAR-3	33.0	40.1
Thymus	2.6	2.3	Ovarian ca. OVCAR-4	5.5	5.4
Spleen	2.9	2.6	Ovarian ca. OVCAR-5	10.9	13.1
Lymph node	5.1	5.2	Ovarian ca. OVCAR-8	17.4	18.3
Colorectal	5.2	3.9	Ovarian ca. IGROV-1	4.5	5.3
Stomach	3.7	5.6	Ovarian ca. (ascites) SK-OV-3	25.7	22.4
Small intestine	1.6	1.3	Uterus	2.7	2.4
Colon ca. SW480	45.4	55.5	Placenta	6.7	10.2
Colon ca.* SW620 (SW480 met)	11.3	11.1	Prostate	0.4	1.4
Colon ca. HT29	13.3	13.3	Prostate ca.* (bone met) PC-3	8.4	11.3
Colon ca. HCT-116	10.5	10.5	Testis	8.1	8.5
Colon ca. CaCo-2	24.0	23.0	Melanoma Hs688(A).T	59.0	86.5
CC Well to Mod Diff	19.1	16.6	Melanoma* (met)	100.0	100.0

(ODO3866)			Hs688(B).T		
Colon ca. HCC-2998	25.7	20.3	Melanoma UACC-62	17.6	19.5
Gastric ca. (liver met) NCI-N87	59.9	62.9	Melanoma M14	16.3	21.9
Bladder	1.8	4.6	Melanoma LOX IMVI	3.6	5.8
Trachea	6.9	5.6	Melanoma* (met) SK-MEL-5	12.9	22.1
Kidney	0.8	0.7	Adipose	5.6	4.5

Table 78. Panel 2.2

Tissue Name	Rel. Exp.(%) Ag2011, Run 174154748	Tissue Name	Rel. Exp.(%) Ag2011, Run 174154748
Normal Colon	24.7	Kidney Margin (OD04348)	68.3
Colon cancer (OD06064)	48.6	Kidney malignant cancer (OD06204B)	25.0
Colon Margin (OD06064)	4.9	Kidney normal adjacent tissue (OD06204E)	7.4
Colon cancer (OD06159)	9.3	Kidney Cancer (OD04450-01)	34.4
Colon Margin (OD06159)	19.5	Kidney Margin (OD04450-03)	18.4
Colon cancer (OD06297-04)	11.7	Kidney Cancer 8120613	9.7
Colon Margin (OD06297-015)	12.5	Kidney Margin 8120614	18.8
CC Gr.2 ascend colon (ODO3921)	17.3	Kidney Cancer 9010320	16.2
CC Margin (ODO3921)	14.2	Kidney Margin 9010321	13.8
Colon cancer metastasis (OD06104)	8.6	Kidney Cancer 8120607	37.1
Lung Margin (OD06104)	8.3	Kidney Margin 8120608	7.0
Colon mets to lung (OD04451- 01)	23.0	Normal Uterus	21.9
Lung Margin (OD04451-02)	32.8	Uterine Cancer 064011	13.7
Normal Prostate	4.8	Normal Thyroid	2.4
Prostate Cancer (OD04410)	4.9	Thyroid Cancer	8.1
Prostate Margin (OD04410)	8.8	Thyroid Cancer A302152	35.4
Normal Ovary	32.3	Thyroid Margin A302153	8.7
Ovarian cancer (OD06283-03)	32.1	Normal Breast	29.7
Ovarian Margin (OD06283-07)	13.8	Breast Cancer	11.9
Ovarian Cancer	19.9	Breast Cancer	47.6
Ovarian cancer (OD06145)	9.2	Breast Cancer (OD04590-01)	25.5
Ovarian Margin (OD06145)	8.6	Breast Cancer Mets (OD04590- 03)	38.4

Ovarian cancer (OD06455-03)	13.0	Breast Cancer Metastasis	30.1
Ovarian Margin (OD06455-07)	2.1	Breast Cancer	41.5
Normal Lung	27.2	Breast Cancer 9100266	9.2
Invasive poor diff. lung adeno (ODO4945-01)	28.5	Breast Margin 9100265	18.2
Lung Margin (ODO4945-03)	15.0	Breast Cancer A209073	14.9
Lung Malignant Cancer (OD03126)	30.4	Breast Margin A2090734	37.6
Lung Margin (OD03126)	15.9	Breast cancer (OD06083)	55.9
Lung Cancer (OD05014A)	39.5	Breast cancer node metastasis (OD06083)	48.6
Lung Margin (OD05014B)	22.1	Normal Liver	10.4
Lung cancer (OD06081)	23.7	Liver Cancer 1026	9.1
Lung Margin (OD06081)	16.8	Liver Cancer 1025	20.7
Lung Cancer (OD04237-01)	9.0	Liver Cancer 6004-T	12.2
Lung Margin (OD04237-02)	41.5	Liver Tissue 6004-N	8.0
Ocular Mel Met to Liver (ODO4310)	100.0	Liver Cancer 6005-T	36.6
Liver Margin (ODO4310)	4.2	Liver Tissue 6005-N	25.0
Melanoma Metastasis	47.0	Liver Cancer	4.5
Lung Margin (OD04321)	28.1	Normal Bladder	18.7
Normal Kidney	12.3	Bladder Cancer	17.2
Kidney Ca, Nuclear grade 2 (OD04338)	18.3	Bladder Cancer	72.7
Kidney Margin (OD04338)	18.0	Normal Stomach	33.4
Kidney Ca Nuclear grade 1/2 (OD04339)	83.5	Gastric Cancer 9060397	9.6
Kidney Margin (OD04339)	10.4	Stomach Margin 9060396	10.4
Kidney Ca, Clear cell type (OD04340)	22.2	Gastric Cancer 9060395	7.6
Kidney Margin (OD04340)	12.7	Stomach Margin 9060394	19.6
Kidney Ca, Nuclear grade 3 (OD04348)	15.7	Gastric Cancer 064005	17.4

Table 79. Panel 2D

Tissue Name	Rel. Exp.(%) Ag1586, Run 162624476	Tissue Name	Rel. Exp.(%) Ag1586, Run 162624476
Normal Colon	34.9	Kidney Margin 8120608	14.2
CC Well to Mod Diff (ODO3866)	28.3	Kidney Cancer 8120613	30.4
CC Margin (ODO3866)	9.2	Kidney Margin 8120614	17.7
CC Gr.2 rectosigmoid	25.9	Kidney Cancer 9010320	57.0

(ODO3868)			
CC Margin (ODO3868)	4.7	Kidney Margin 9010321	40.9
CC Mod Diff (ODO3920)	55.5	Normal Uterus	10.4
CC Margin (ODO3920)	14.2	Uterine Cancer 064011	28.9
CC Gr.2 ascend colon (ODO3921)	62.9	Normal Thyroid	8.4
CC Margin (ODO3921)	12.1	Thyroid Cancer	16.7
CC from Partial Hepatectomy (ODO4309) Mets	41.5	Thyroid Cancer A302152	24.7
Liver Margin (ODO4309)	13.6	Thyroid Margin A302153	17.7
Colon mets to lung (OD04451-01)	18.0	Normal Breast	60.3
Lung Margin (OD04451-02)	25.5	Breast Cancer	24.1
Normal Prostate 6546-1	17.0	Breast Cancer (OD04590-01)	47.0
Prostate Cancer (OD04410)	33.7	Breast Cancer Mets (OD04590-03)	72.7
Prostate Margin (OD04410)	28.9	Breast Cancer Metastasis	37.4
Prostate Cancer (OD04720-01)	33.7	Breast Cancer	36.9
Prostate Margin (OD04720-02)	45.7	Breast Cancer	65.1
Normal Lung	80.7	Breast Cancer 9100266	39.8
Lung Met to Muscle (ODO4286)	100.0	Breast Margin 9100265	31.2
Muscle Margin (ODO4286)	21.5	Breast Cancer A209073	49.0
Lung Malignant Cancer (OD03126)	57.8	Breast Margin A2090734	44.8
Lung Margin (OD03126)	61.6	Normal Liver	4.5
Lung Cancer (OD04404)	70.2	Liver Cancer	2.6
Lung Margin (OD04404)	34.2	Liver Cancer 1025	4.7
Lung Cancer (OD04565)	87.7	Liver Cancer 1026	18.3
Lung Margin (OD04565)	23.8	Liver Cancer 6004-T	7.6
Lung Cancer (OD04237-01)	41.5	Liver Tissue 6004-N	12.0
Lung Margin (OD04237-02)	34.2	Liver Cancer 6005-T	12.1
Ocular Mel Met to Liver (ODO4310)	97.3	Liver Tissue 6005-N	5.7
Liver Margin (ODO4310)	5.0	Normal Bladder	38.2
Melanoma Metastasis	87.7	Bladder Cancer	21.3
Lung Margin (OD04321)	56.3	Bladder Cancer	46.0
Normal Kidney	30.1	Bladder Cancer (OD04718-01)	96.6
Kidney Ca, Nuclear grade 2 (OD04338)	46.7	Bladder Normal Adjacent (OD04718-03)	29.5
Kidney Margin (OD04338)	14.8	Normal Ovary	21.5
Kidney Ca Nuclear grade 1/2 (OD04339)	52.1	Ovarian Cancer	73.7
Kidney Margin (OD04339)	20.3	Ovarian Cancer (OD04768-07)	48.3

Kidney Ca, Clear cell type (OD04340)	49.0	Ovary Margin (OD04768-08)	18.8
Kidney Margin (OD04340)	23.2	Normal Stomach	13.9
Kidney Ca, Nuclear grade 3 (OD04348)	42.6	Gastric Cancer 9060358	6.7
Kidney Margin (OD04348)	28.9	Stomach Margin 9060359	13.2
Kidney Cancer (OD04622-01)	50.7	Gastric Cancer 9060395	28.3
Kidney Margin (OD04622-03)	8.6	Stomach Margin 9060394	18.0
Kidney Cancer (OD04450-01)	21.8	Gastric Cancer 9060397	45.4
Kidney Margin (OD04450-03)	18.2	Stomach Margin 9060396	10.4
Kidney Cancer 8120607	25.0	Gastric Cancer 064005	48.3

Table 80. Panel 4D

Tissue Name	Rel. Exp.(%) Ag2011, Run 160997385	Tissue Name	Rel. Exp.(%) Ag2011, Run 160997385
Secondary Th1 act	4.7	HUVEC IL-1beta	2.0
Secondary Th2 act	6.4	HUVEC IFN gamma	4.0
Secondary Tr1 act	8.6	HUVEC TNF alpha + IFN gamma	5.0
Secondary Th1 rest	0.6	HUVEC TNF alpha + IL4	8.4
Secondary Th2 rest	1.7	HUVEC IL-11	3.5
Secondary Tr1 rest	1.7	Lung Microvascular EC none	13.0
Primary Th1 act	14.0	Lung Microvascular EC TNFalpha + IL-1beta	15.3
Primary Th2 act	7.7	Microvascular Dermal EC none	23.2
Primary Tr1 act	12.9	Microvascular Dermal EC TNFalpha + IL-1beta	17.3
Primary Th1 rest	3.3	Bronchial epithelium TNFalpha + IL1beta	4.5
Primary Th2 rest	2.3	Small airway epithelium none	16.0
Primary Tr1 rest	2.0	Small airway epithelium TNFalpha + IL-1beta	100.0
CD45RA CD4 lymphocyte act	6.5	Coronary artery SMC rest	15.7
CD45RO CD4 lymphocyte act	5.3	Coronary artery SMC TNFalpha + IL-1beta	11.1
CD8 lymphocyte act	3.3	Astrocytes rest	25.3
Secondary CD8 lymphocyte rest	7.2	Astrocytes TNFalpha + IL-1beta	21.6
Secondary CD8 lymphocyte act	3.0	KU-812 (Basophil) rest	8.4
CD4 lymphocyte none	1.6	KU-812 (Basophil)	39.5

		PMA/ionomycin	
2ry Th1/Th2/Tr1_anti-CD95 CH11	0.3	CCD1106 (Keratinocytes) none	35.1
LAK cells rest	19.1	CCD1106 (Keratinocytes) TNFalpha + IL-1beta	5.9
LAK cells IL-2	3.1	Liver cirrhosis	0.9
LAK cells IL-2+IL-12	6.5	Lupus kidney	1.3
LAK cells IL-2+IFN gamma	9.8	NCI-H292 none	42.3
LAK cells IL-2+ IL-18	5.9	NCI-H292 IL-4	90.1
LAK cells PMA/ionomycin	8.7	NCI-H292 IL-9	58.2
NK Cells IL-2 rest	1.7	NCI-H292 IL-13	33.9
Two Way MLR 3 day	9.3	NCI-H292 IFN gamma	30.4
Two Way MLR 5 day	7.4	HPAEC none	5.8
Two Way MLR 7 day	2.0	HPAEC TNF alpha + IL-1 beta	12.9
PBMC rest	1.7	Lung fibroblast none	23.8
PBMC PWM	12.5	Lung fibroblast TNF alpha + IL-1 beta	10.7
PBMC PHA-L	5.4	Lung fibroblast IL-4	59.0
Ramos (B cell) none	0.5	Lung fibroblast IL-9	40.6
Ramos (B cell) ionomycin	0.9	Lung fibroblast IL-13	31.0
B lymphocytes PWM	15.6	Lung fibroblast IFN gamma	65.5
B lymphocytes CD40L and IL-4	5.8	Dermal fibroblast CCD1070 rest	37.4
EOL-1 dbcAMP	3.5	Dermal fibroblast CCD1070 TNF alpha	50.0
EOL-1 dbcAMP PMA/ionomycin	60.3	Dermal fibroblast CCD1070 IL-1 beta	19.6
Dendritic cells none	17.6	Dermal fibroblast IFN gamma	15.0
Dendritic cells LPS	32.5	Dermal fibroblast IL-4	43.8
Dendritic cells anti-CD40	21.0	IBD Colitis 2	0.3
Monocytes rest	0.1	IBD Crohn's	0.8
Monocytes LPS	8.4	Colon	5.3
Macrophages rest	34.2	Lung	15.0
Macrophages LPS	11.3	Thymus	5.8
HUVEC none	6.5	Kidney	11.4
HUVEC starved	9.3		

Panel 1.3D Summary: Ag1586/Ag2011

Two experiments with the same probe and primer set produce results that are in excellent agreement. NOV12 appears to be expressed largely in cancer cell lines, with highest

expression in a melanoma cell line (CTs=26-28). Of note is the expression associated with colon cancer cell lines as well as melanoma cell lines. Thus, the expression of this gene could be used to distinguish these samples from other samples on the panel. Moreover, therapeutic modulation of this gene, through the use of small molecule drugs, antibodies or protein therapeutics might be of use in the treatment of colon cancer or melanoma.

This gene is modestly expressed in a variety of metabolic tissues including pancreas, adrenal, thyroid, pituitary, fetal liver, and adipose. Thus, this gene product may be an antibody target for the treatment of metabolic disease, including obesity and diabetes, in any or all of these tissues. In addition, NOV12 is differentially expressed in fetal (CT values = 26-28) versus adult heart (CT values = 31-33), and in fetal (CT values = 26-28) versus adult skeletal muscle (CT values = 32-33), and may be used to differentiate between the adult and fetal sources of these tissues. Furthermore, the higher levels of expression in the fetal tissues suggest that the SC132340676_A gene product may be involved in the development of heart and skeletal muscle tissue. Thus, therapeutic modulation of the expression or function of the protein encoded by the SC132340676_A gene may be beneficial in the treatment of diseases that result in weak or dystrophic heart or skeletal muscle tissue, including ardiomyopathy, atherosclerosis, hypertension, congenital heart defects, aortic stenosis, atrial septal defect (ASD), atrioventricular (A-V) canal defect, ductus arteriosus, pulmonary stenosis, subaortic stenosis, ventricular septal defect (VSD), valve diseases, muscular dystrophy, Lesch-Nyhan syndrome, and myasthenia gravis.

This gene represents a novel protein with homology to a plexin that is expressed at moderate to high levels in all brain regions examined. Plexins act as receptors for semaphorins in the CNS. The interactions of the semaphorins and their receptors are critical for axon guidance. Therefore, this gene product may be useful as a drug target in clinical conditions where axonal growth and/or compensatory synaptogenesis are desirable (spinal cord or head trauma, stroke, or neurodegenerative diseases such as Alzheimer's, Parkinson's, or Huntington's disease).

References:

1. Pasterkamp RJ, Ruitenber MJ, Verhaagen J. Semaphorins and their receptors in olfactory axon guidance. *Cell Mol Biol (Noisy-le-grand)* 1999 Sep;45(6):763-79

The mammalian olfactory system is capable of discriminating among a large variety of odor molecules and is therefore essential for the identification of food, enemies and mating partners. The assembly and maintenance of olfactory connectivity have been shown to depend

on the combinatorial actions of a variety of molecular signals, including extracellular matrix, cell adhesion and odorant receptor molecules. Recent studies have identified semaphorins and their receptors as putative molecular cues involved in olfactory pathfinding, plasticity and regeneration. The semaphorins comprise a large family of secreted and transmembrane axon guidance proteins, being either repulsive or attractive in nature. Neuropilins were shown to serve as receptors for secreted class 3 semaphorins, whereas members of the plexin family are receptors for class 1 and V (viral) semaphorins. The present review will discuss a role for semaphorins and their receptors in the establishment and maintenance of olfactory connectivity.

2. Murakami Y, Suto F, Shimizu M, Shinoda T, Kameyama T, Fujisawa H. Differential expression of plexin-A subfamily members in the mouse nervous system. *Dev Dyn* 2001 Mar;220(3):246-58

Plexins comprise a family of transmembrane proteins (the plexin family) which are expressed in nervous tissues. Some plexins have been shown to interact directly with secreted or transmembrane semaphorins, while plexins belonging to the A subfamily are suggested to make complexes with other membrane proteins, neuropilins, and propagate chemorepulsive signals of secreted semaphorins of class 3 into cells or neurons. Despite that much information has been gathered on the plexin-semaphorin interaction, the role of plexins in the nervous system is not well understood. To gain insight into the functions of plexins in the nervous system, we analyzed spatial and temporal expression patterns of three members of the plexin-A subfamily (plexin-A1, -A2, and -A3) in the developing mouse nervous system by in situ hybridization analysis in combination with immunohistochemistry. We show that the three plexins are differentially expressed in sensory receptors or neurons in a developmentally regulated manner, suggesting that a particular plexin or set of plexins is shared by neuronal elements and functions as the receptor for semaphorins to regulate neuronal development.

Panel 2.2 Summary: Ag2011

The expression of NOV12 appears to be highest in a sample derived from a melanoma metastasis. In addition, there is substantial expression in another melanoma sample. These results are in agreement with the results seen in Panel 1.3D, with significant expression detected in melanoma cell lines. Thus, the expression of this gene could be used to distinguish melanoma from other cancer types in this panel. Moreover, therapeutic modulation of this gene, through the use of small molecule drugs, antibodies or protein therapeutics might be of use in the treatment of melanoma.

Panel 2D Summary: Ag1586

The expression of NOV12 is highest in a sample derived from a metastasis of lung cancer. Thus, the expression of this gene could be used to distinguish this sample from the others in the panel. In addition, there is substantial expression in bladder cancer, when compared to its normal adjacent tissue, as well as in two samples of melanoma. Thus, the expression of this gene could be used to distinguish this bladder cancer from its normal adjacent tissue, or these melanomas from other samples. Moreover, therapeutic modulation of this gene, through the use of small molecule drugs, antibodies or protein therapeutics might be of use in the treatment of lung cancer, bladder cancer or melanoma.

Panel 4D Summary: Ag2011

Significant expression of the NOV12 transcript is found in small airway epithelium upon treatment with the pro-inflammatory cytokines TNF- α and IL-1 β (CT= 26.5), the mucoc-epidermoid cell line H 292 treated with IL-4 or IL-9, and in lung fibroblasts treated with IFN- γ or IL-4. The constitutive expression of this transcript in these tissues is highly up-regulated by pro-inflammatory cytokines or in conditions reflecting a Th2 mediated mechanism. Therefore, modulation of the expression of the protein encoded by this transcript could be useful for the treatment of lung inflammatory diseases that result from infection of the lung (bronchitis, pneumonia) and for the treatment of Th2 –mediated lung disease such as asthma or COPD. Significant expression of this transcript is also found in eosinophils upon PMA and ionomycin treatment, conditions that lead to production of eosinophil specific mediators. This production could contribute to the pathologies associated with asthma, other atopic diseases and inflammatory bowel disease. This gene encodes a novel protein with homology to members of the plexin family, a family of transmembrane proteins which act as receptors for semaphorins. In neurons, semaphorins provide essential attractive and repulsive cues that are necessary for axon guidance. The description of the interaction of plexin with tyrosine kinase in the fetal lung suggests that this protein may play a role not only in morphogenesis but also in proliferation of activation. (See reference below.) Therefore, modulation of the expression of this protein by either antibody or small molecules could be beneficial for the treatment of inflammatory lung, bowel and skin diseases.

Reference:

1. Cell 1999 Oct 1;99(1):71-80

Plexins are a large family of receptors for transmembrane, secreted, and GPI-anchored semaphorins in vertebrates.

Tamagnone L, Artigiani S, Chen H, He Z, Ming GI, Song H, Chedotal A, Winberg ML, Goodman CS, Poo M, Tessier-Lavigne M, Comoglio PM.

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5 In *Drosophila*, plexin A is a functional receptor for semaphorin-1a. Here we show that
the human plexin gene family comprises at least nine members in four subfamilies. Plexin-B1
is a receptor for the transmembrane semaphorin Sema4D (CD100), and plexin-C1 is a receptor
for the GPI-anchored semaphorin Sema7A (Sema-K1). Secreted (class 3) semaphorins do not
bind directly to plexins, but rather plexins associate with neuropilins, coreceptors for these
10 semaphorins. Plexins are widely expressed: in neurons, the expression of a truncated plexin-
A1 protein blocks axon repulsion by Sema3A. The cytoplasmic domain of plexins associates
with a tyrosine kinase activity. Plexins may also act as ligands mediating repulsion in
epithelial cells in vitro. We conclude that plexins are receptors for multiple (and perhaps all)
classes of semaphorins, either alone or in combination with neuropilins, and trigger a novel
15 signal transduction pathway controlling cell repulsion

PMID: 10520995

Example 3. SNP analysis of NOVX clones

SeqCalling™ Technology: cDNA was derived from various human samples
representing multiple tissue types, normal and diseased states, physiological states, and
20 developmental states from different donors. Samples were obtained as whole tissue, cell lines,
primary cells or tissue cultured primary cells and cell lines. Cells and cell lines may have been
treated with biological or chemical agents that regulate gene expression for example, growth
factors, chemokines, steroids. The cDNA thus derived was then sequenced using CuraGen's
proprietary SeqCalling technology. Sequence traces were evaluated manually and edited for
25 corrections if appropriate. cDNA sequences from all samples were assembled with themselves
and with public ESTs using bioinformatics programs to generate CuraGen's human SeqCalling
database of SeqCalling assemblies. Each assembly contains one or more overlapping cDNA
sequences derived from one or more human samples. Fragments and ESTs were included as
components for an assembly when the extent of identity with another component of the
30 assembly was at least 95% over 50 bp. Each assembly can represent a gene and/or its variants
such as splice forms and/or single nucleotide polymorphisms (SNPs) and their combinations.

Variant sequences are included in this application. A variant sequence can include a
single nucleotide polymorphism (SNP). A SNP can, in some instances, be referred to as a

"cSNP" to denote that the nucleotide sequence containing the SNP originates as a cDNA. A SNP can arise in several ways. For example, a SNP may be due to a substitution of one nucleotide for another at the polymorphic site. Such a substitution can be either a transition or a transversion. A SNP can also arise from a deletion of a nucleotide or an insertion of a nucleotide, relative to a reference allele. In this case, the polymorphic site is a site at which one allele bears a gap with respect to a particular nucleotide in another allele. SNPs occurring within genes may result in an alteration of the amino acid encoded by the gene at the position of the SNP. Intragenic SNPs may also be silent, however, in the case that a codon including a SNP encodes the same amino acid as a result of the redundancy of the genetic code. SNPs occurring outside the region of a gene, or in an intron within a gene, do not result in changes in any amino acid sequence of a protein but may result in altered regulation of the expression pattern for example, alteration in temporal expression, physiological response regulation, cell type expression regulation, intensity of expression, stability of transcribed message.

Method of novel SNP Identification: SNPs are identified by analyzing sequence assemblies using CuraGen's proprietary SNPTool algorithm. SNPTool identifies variation in assemblies with the following criteria: SNPs are not analyzed within 10 base pairs on both ends of an alignment; Window size (number of bases in a view) is 10; The allowed number of mismatches in a window is 2; Minimum SNP base quality (PHRED score) is 23; Minimum number of changes to score an SNP is 2/assembly position. SNPTool analyzes the assembly and displays SNP positions, associated individual variant sequences in the assembly, the depth of the assembly at that given position, the putative assembly allele frequency, and the SNP sequence variation. Sequence traces are then selected and brought into view for manual validation. The consensus assembly sequence is imported into CuraTools along with variant sequence changes to identify potential amino acid changes resulting from the SNP sequence variation. Comprehensive SNP data analysis is then exported into the SNPCalling database.

Method of novel SNP Confirmation: SNPs are confirmed employing a validated method known as Pyrosequencing (Pyrosequencing, Westborough, MA). Detailed protocols for Pyrosequencing can be found in: Alderborn et al. Determination of Single Nucleotide Polymorphisms by Real-time Pyrophosphate DNA Sequencing. (2000). *Genome Research*. 10, Issue 8, August. 1249-1265. In brief, Pyrosequencing is a real time primer extension process of genotyping. This protocol takes double-stranded, biotinylated PCR products from genomic DNA samples and binds them to streptavidin beads. These beads are then denatured producing single stranded bound DNA. SNPs are characterized utilizing a technique based on an indirect bioluminometric assay of pyrophosphate (PPi) that is released from each dNTP upon DNA

chain elongation. Following Klenow polymerase-mediated base incorporation, PPi is released and used as a substrate, together with adenosine 5'-phosphosulfate (APS), for ATP sulfurylase, which results in the formation of ATP. Subsequently, the ATP accomplishes the conversion of luciferin to its oxi-derivative by the action of luciferase. The ensuing light output becomes proportional to the number of added bases, up to about four bases. To allow processivity of the method dNTP excess is degraded by apyrase, which is also present in the starting reaction mixture, so that only dNTPs are added to the template during the sequencing. The process has been fully automated and adapted to a 96-well format, which allows rapid screening of large SNP panels. The DNA and protein sequences for the novel single nucleotide polymorphic variants are reported. Variants are reported individually but any combination of all or a select subset of variants are also included. In addition, the positions of the variant bases and the variant amino acid residues are underlined.

Results

Variants are reported individually but any combination of all or a select subset of variants are also included as contemplated NOVX embodiments of the invention.

NOV6 SNP data:

NOV6 has two SNP variants, whose variant positions for their nucleotide and amino acid sequences is numbered according to SEQ ID NOs:17 and 18, respectively. The nucleotide sequence of the NOV6 variants differs as shown in Table 81.

Table 81. cSNP and Coding Variants for NOV6				
NT Position of cSNP	Wild Type NT	Variant NT	Amino Acid position	Amino Acid Change
446	T	C	No change	No change
553	A	G	No change	No change

NOV8 SNP data:

NOV8 has two SNP variants, whose variant positions for their nucleotide and amino acid sequences is numbered according to SEQ ID NOs:21 and 22, respectively. The nucleotide sequence of the NOV8 variants differs as shown in Table 82.

Table 82. cSNP and Coding Variants for NOV8				
NT Position of cSNP	Wild Type NT	Variant NT	Amino Acid position	Amino Acid Change
564	G	A	109	G->D
976	T	G	No change	No change

NOV9 SNP data:

NOV 9 has two SNP variants, whose variant positions for their nucleotide and amino acid sequences is numbered according to SEQ ID NOs:23 and 24 , respectively. The nucleotide sequence of the NOV9 variants differs as shown in Table 83.

Table 83. cSNP and Coding Variants for NOV9				
NT Position of cSNP	Wild Type NT	Variant NT	Amino Acid position	Amino Acid Change
111	A	C	No change	No change
200	A	G	62	K→R

5 **NOV10 SNP data:**

NOV10 has two SNP variants, whose variant positions for their nucleotide and amino acid sequences is numbered according to SEQ ID NOs:25 and 26, respectively. The nucleotide sequence of the NOV10 variants differs as shown in Table 84.

Table 84. cSNP and Coding Variants for NOV10				
NT Position of cSNP	Wild Type NT	Variant NT	Amino Acid position	Amino Acid Change
2129	C	T	No change	No change
2450	T	C	No change	No change

10

NOV11 SNP data:

NOV11a has three SNP variants, whose variant positions for their nucleotide and amino acid sequences is numbered according to SEQ ID NOs:27 and 28, respectively. The nucleotide sequence of the NOV11a variant differs as shown in Table 85.

15

Table 85. cSNP and Coding Variants for NOV11a				
NT Position of cSNP	Wild Type NT	Variant NT	Amino Acid position	Amino Acid Change
122	C	G	No change	No change
208	G	C	No change	No change
372	C	T	97	P->L
482	A	G	134	N->D

Example 4. In-frame Cloning

NOV1b

20 For NOV1b, the cDNA coding for the DOMAIN of NOV1a (CG50718-02) from residues 18 to 917 was targeted for “in-frame” cloning by PCR. The PCR template was based on the previously identified plasmid, when available, or on human cDNA(s).

Table 86. Oligonucleotide primers used to clone the target cDNA sequence:

Primers	Sequences
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Repeat steps b-d 15 times

- e) 96°C 15 seconds denaturation
- f) 60°C 30 seconds, primer annealing
- g) 72°C 6 minutes extension

Repeat steps e-g 29 times

- e) 72°C 10 minutes final extension

PCR condition 2:

- a) 96°C 3 minutes
- b) 96°C 15 seconds denaturation
- c) 76°C 30 seconds, primer annealing, reducing the temperature by 1 °C per cycle
- d) 72°C 4 minutes extension

Repeat steps b-d 34 times

- e) 72°C 10 minutes final extension

An amplified product was detected by agarose gel electrophoresis. The fragment was gel-purified and ligated into the pCR2.1 vector (Invitrogen, Carlsbad, CA) following the manufacturer's recommendation. Twelve clones per PCR reaction were picked and sequenced. The inserts were sequenced using vector-specific M13 Forward and M13 Reverse primers and the gene-specific primers in Tables 88 and 89.

Table 88. Gene-specific Primers

NOV	Primers	Sequences
NOV11c	SF1	GCCCTCCCGGTCCAGGTC (SEQ ID NO:200)
	SF2	GGCGACGGCACCAGCATGT (SEQ ID NO:201)
	SR1	GCCTGGCCTGCCGGTTCT (SEQ ID NO:202)
	SR2	CATGAGCACGTGGTAAGCG (SEQ ID NO:203)

Table 89. Gene-specific Primers

NOV	Primers	Sequences
NOV1b	SF1	GTGCTGGCATTGGAGTGTTTAGTG (SEQ ID NO:204)
	SF2	ATCAAGCACGTTGACACAGAATGAG (SEQ ID NO:205)
	SF3	GCATTCACCTAACCTAACACCATTTACA (SEQ ID NO:206)
	SF4	GTTGAGCAGAGATGTCGTCTGACCTTC (SEQ ID NO:207)
	SF5	GGGATCCTCCAGATCCTGTATTTTT (SEQ ID NO:208)
	SF6	TGAAGAACACATCAACAACAGACATAA (SEQ ID NO:209)
	SR1	ACTGTTTTGAGCAGCTACCTTAATTTC (SEQ ID NO:210)
	SR2	CTTGATGAATGTGTGGTACGCGAT (SEQ ID NO:211)
	SR3	GTGAATGCAAACTGAGGTCTTTTGT (SEQ ID NO:212)
	SR4	CCTCATATAATCCTACCATGGCTGTACT (SEQ ID NO:213)
	SR5	GAGGATCCCAGTGTAATACTTCTG (SEQ ID NO:214)
	SR6	TAGCACTTCATAAGCAATAATGATCCC (SEQ ID NO:215)
	SR7	TGAGTGTACTAGCAGACCTCAATGAT (SEQ ID NO:216)

OTHER EMBODIMENTS

Although particular embodiments have been disclosed herein in detail, this has been done by way of example for purposes of illustration only, and is not intended to be limiting with respect to the scope of the appended claims, which follow. In particular, it is contemplated by the inventors that various substitutions, alterations, and modifications may be made to the invention without departing from the spirit and scope of the invention as defined by the claims. The choice of nucleic acid starting material, clone of interest, or library type is believed to be a matter of routine for a person of ordinary skill in the art with knowledge of the embodiments described herein. Other aspects, advantages, and modifications considered to be within the scope of the following claims.